Chemistry Lib.
OCT 2 3 1934

The Most Serious Difficulty To-day in Practically All Activities—Legislation, Education and Otherwise—Is Not Altogether That Conditions Are Bad, but There Is a Deficiency in Concentration and a Lack of Certainty as to What Is to Happen Next.

Vol. XXIII, No. 9 SEPTEMBER, 1934

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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THE 83rd ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN PORTLAND, ORE., IN 1935.

The 1935 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Portland.

Entered as second-class Matter, January 23, 1917, at the Post Office at Easton, Pa., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in section 1103. Act of October 3, 1917; authorized July 10, 1918.

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Approving the objects of the American Pharmaceutical Association, I hereby apply for membership in the Association and subscribe for the "Journal of the American Pharmaceutical Association," and enclose $5.00 as annual membership dues, $4.00 of which is for a year's subscription to the Journal.

Name in Full.....

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This application with the first year's payment of $5.00 may be sent to the Chairman of the Membership Committee, the Secretary or any officer of the A. Ph. A.

E. F. KELLY, Secretary,
2215 Constitution Ave.,
Washington, D. C.

PHARMACY WEEK.

EXCERPTS FROM CHAIRMAN ANTON HOGSTAD'S MESSAGE.

THE secretaries of our various pharmaceutical organizations are urged to secure a word of greeting from the Governors of the respective states. Do not delay in this matter. In previous years we have secured some worth-while words of greetings from State Executives which supplement in a nice manner the President's proclamation.

PHARMACY WEEK MAPS.

Secretary E. L. Newcomb, National Wholesale Druggists' Association, has informed the National Pharmacy Week Executive Committee that he has a goodly supply of beautiful lithographed Pharmacy Week maps on hand, including that interesting map dealing with the medicinal plants of the United States.

These maps can be secured through your service wholesaler or by writing to Dr. E. L. Newcomb at 51 Maiden Lane, New York City. During the course of the past few years hundreds of requests have been received for these maps from High Schools and Colleges. Here is a splendid opportunity for the retail pharmacist to assist the High School or College in the community by presenting these institutions with copies of these maps. They will accomplish a great deal in bringing the message of Pharmacy to those attending these institutions.

"OPEN HOUSE" AT THE COLLEGES OF PHARMACY.

The Colleges of Pharmacy are in an excellent position to render the profession a real service during Pharmacy Week by having "Open House" at the college in question, and to invite all members of the faculty and student body of the entire college or university as well as to extend invitations to members of allied professions and to the laity.

MIMEOGRAPHED COPIES OF TALKS AVAILABLE.

As in former years, the National Pharmacy Week Executive Committee will distribute upon request some twenty or more human interest appeal stories in mimeographed form. Arrange now with the secretaries of your various community organizations for the presentation of one or more of these interesting stories. Simply address the Chairman at 2215 Constitution Ave., Washington, D. C., and copies will be sent you free of charge.

WINDOW DISPLAYS.

Many pharmacists are prone to feel that it requires considerable money as well as an expenditure of considerable time for the preparation of a professional window display. This is not altogether true, for in many cases all that is needed is a captivating title, a few materials, a few well-worded show cards, all of which, if properly arranged, will bring into being a dramatic and interesting display.

Have a photograph made of your window display, preferably by a commercial photographer. The photographs best set forth the detail if they measure at least eight by ten inches. The photographs should be submitted to the secretary of your State pharmaceutical organization on or before December 31, 1934. The State Secretary in turn will select the State winner and will then submit the prize-winning photograph for the state in question to the National Pharmacy Week Window Display Contest Committee. The national winner will then be selected by this Committee which for 1934 will comprise outstanding personages in the Drug Trade Industry of New Orleans.

The 1934 Pharmacy Week observance is just around the corner. Let us impress the members of allied professions as well as the laity that Pharmacy is a profession, that you are glad of the fact that you are a pharmacist and that you have taken an active part in making the 10th annual observance one long to be remembered. The year 1934 marked the dedication of the American Institute of Pharmacy. . . . your Institute at Washington, D. C. In many respects the year 1934 has meant a great deal to Pharmacy—let us make the week, October 8th–13th, a Pharmacy Week in every respect.

CHARLES H. EVANS.

Chemistry
Direct
10-23-34

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXIII SEPTEMBER, 1934 No. 9

CHARLES H. EVANS.

Charles Hall Evans was born December 15, 1895, at Norwood, Ga., the son of William T. and Mary Hall Evans. He received his early education in the public schools and Warrenton High School. In 1915, he graduated in pharmacy from Mercer University, Macon, Ga., and is a member of Eta Chapter, Sigma Nu and the Alembic (Science) Club. After graduation he entered the pharmacy of his father and was admitted to partnership in the three stores operated by the firm in Warrenton, Norwood and Harlem; after the death of his father, in 1926, he became sole owner; he is now operating two pharmacies in Warrenton.

Mr. Evans has been a member of the Georgia State Board of Pharmacy since 1928; from 1932 to 1934 he served as vice-president and chairman of District No. 7, and this year he was elected president of the National Association of Boards of Pharmacy. He was chairman of the Georgia Board of Pharmacy when the college prerequisite amendment was enacted, and is chairman of the Legal Committee of Georgia Pharmaceutical Association in charge of a revision of the pharmacy law for presentation to the 1935 session of the legislature. He is a member of the Board of Directors of Georgia Pharmaceutical Association.

Mr. Evans takes an active interest in civic affairs and is a past-president of Warrenton Chamber of Commerce, is chairman of the Board of Education of Warrenton public schools and of a number of other various local organizations. He is a member of the Warrenton Methodist Church, a steward, trustee and the treasurer.

February 6, 1917, Mr. Evans married Miss Sarah Rodgers Lang of Danielsville, Ga.; they have one son.

OFFICERS NATIONAL ASSOCIATION BOARDS OF PHARMACY.

President, C. H. Evans, Warrenton, Ga.; *Honorary President*, F. W. Hancock, Oxford, N. C.; *Vice-Presidents*, George Moulton, New Hampshire; John Woodside, Pennsylvania; E. V. Zoeller, North Carolina; Albert Ely, Kentucky; Wm. Muesing, Minnesota; C. M. Brewer, Oklahoma; R. C. Schultz, Wyoming; R. W. Fleming, Nevada; *Secretary*, H. C. Christensen, 130 N. Wells St., Chicago, Ill.; *Treasurer*, J. W. Gayle, Frankfort, Ky.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

OUR STAND ON FEDERAL DRUG LEGISLATION.

BY ROBERT P. FISCHELIS.*

LAST year, due to lack of knowledge of the facts or misinformation, the profession of pharmacy was classified in the minds of many laymen and members of other professions as an opponent of new legislation to strengthen the Federal food and drug law. Out of the maze of propaganda for and against the enactment of more stringent regulations to govern the manufacture, distribution and advertising of food, drug and cosmetic products, we emerged, in the eyes of the public, as weak proponents of obviously necessary reforms and as strong opponents of regulatory measures containing the necessary "teeth" to enforce the reforms which we really favored. It is unfortunate that the AMERICAN PHARMACEUTICAL ASSOCIATION, which has prided itself since its organization in 1851, upon being a champion of legislation to suppress the distribution of inferior, adulterated and deteriorated drugs, should have been placed in this position. Year after year, the ASSOCIATION has placed itself on record against fraudulent practices in the manufacture, sale and advertising of drugs and cosmetics. It is also on record in favor of at least partial formula disclosure of so-called patent medicines and other secret remedies.

In all of the publicity attending the various hearings on proposed drug and cosmetic legislation last year, the voice of the AMERICAN PHARMACEUTICAL ASSOCIATION was not heard because it was submerged in the unified opposition offered by the "drug trade" to certain features of the legislation proposed by the Government to stamp out evils which have crept into the food, drug and cosmetic industries and with which the Government is unable to cope under existing law.

We can very well be proud of the efforts made by the AMERICAN PHARMACEUTICAL ASSOCIATION in its attempt to present pharmacal opinion in unified form through the National Drug Trade Conference which the ASSOCIATION called into being. However, when interests represented in the Conference indulge in the type of propaganda which was used last year to defeat proposed food, drug and cosmetic legislation, we must take steps to make our position clear and let it be understood in no uncertain terms that we are not a party to such a program.

The new Congress will undoubtedly give attention to food, drug and cosmetic legislation. The AMERICAN PHARMACEUTICAL ASSOCIATION is convinced of the necessity for constructive and, in some respects, drastic revision of existing food and drug laws. As the acknowledged representative of professional pharmacy in the United States, it will endeavor to lend the full weight of its influence toward the enactment of reasonable, effective and enforceable legislation which will protect the consuming public against fraud of all kinds in the drug and cosmetic industry.

It is recognized that laws which do not provide for adequate enforcement machinery had better not be written into the statute books. The law-abiding citizen must put up with many irksome restrictions of his liberties in order to make it possible to apprehend the enemies of society. The food, drug and cosmetic industries cannot expect the Government to protect the public against exploitation by the unscrupulous, with its incident protection of the honest manufacturer and distributor, unless sufficient power is granted to make law enforcement a fact and not a farce.

* President, AMERICAN PHARMACEUTICAL ASSOCIATION.

AN IMPORTANT MESSAGE.

A prominent American pharmaceutical manufacturing firm, which has contributed on several occasions to the Headquarters Building Fund in increasing amounts, has recently made without any restriction as to its use, the largest single contribution so far received by the ASSOCIATION and has paid it in full.

In their letter of transmittal this firm made certain observations and statements with respect to present conditions in the practice of pharmacy, the changes that are necessary to enable the profession to render the public health service expected of it, the urgency of dealing effectively with the present situation and the part that the ASSOCIATION is prepared and should be equipped to take in this important work, which are so clear and forceful that permission has been obtained to quote them, as follows:

"We know of no organization that can, provided that it is adequately financed, contribute more to build up the reputation and prestige of pharmacy, and improve the service of pharmacy in the public health field than the AMERICAN PHARMACEUTICAL ASSOCIATION. Our confidence is justified by the past achievements and efforts of the ASSOCIATION: these have ever been sincere, helpful and altruistic. Unfortunately, however, they were limited through lack of proper quarters for the ASSOCIATION and sufficient financial support. Now at last one of these handicaps has been removed through the ASSOCIATION'S occupancy of its beautiful new structure.

"There remains the urgent need to provide a maintenance fund so that the AMERICAN PHARMACEUTICAL ASSOCIATION may achieve its objectives of service to the profession of pharmacy and to the public.

"We deemed it a duty and privilege to contribute to the New Building Fund of the ASSOCIATION, and now we desire to give support to the ASSOCIATION'S activities. Accordingly, we enclose our check for fifty thousand dollars for such use as your Council may decide upon.

"May we add that we do not consider this subscription a gift. Instead, we look upon it as a subsidizing of work to improve the economic side of pharmacy through building up its prestige and improving its service. This is work which we, as an individual concern or in coöperation with a group of manufacturers, are unable to carry on. Unless the work is conducted effectively, we fear that the present confusion in pharmacy may culminate in the death of pharmacy. We feel, therefore, that in subsidizing the work of the ASSOCIATION we are aiding the profession of pharmacy and the public, and, moreover, safeguarding the future of our own company, the pharmaceutical industry and the retail pharmacist.

"We earnestly hope that the efforts of your Council to raise a maintenance fund may result in quick provision of the funds you need, for we believe the situation in the field of pharmacy and the services your ASSOCIATION will render require immediate action."

This estimate of the undesirable conditions which threaten the future of pharmacy and the urgent need for correcting them, is so sound and so correctly expressed that every one interested in promoting pharmaceutical progress should have the opportunity to read it.—H. A. B. DUNNING, *Chairman, Committee on Maintenance Fund*

AN OPEN LETTER TO RETAIL PHARMACISTS ON THE AMERICAN INSTITUTE OF PHARMACY.

THE AMERICAN PHARMACEUTICAL ASSOCIATION does not need a million-dollar maintenance fund for the American Institute of Pharmacy immediately, and could probably fulfil its mission quite satisfactorily with half the amount mentioned, but it does require, within the very near future, approximately $100,000.00.

The money which has been expended for the land, the building, its equipment, furnishings, planting, every expense included, amounts to $590,000.00. All but $76,000.00 of these costs have been met by the contributions received. This $76,000.00 must be liquidated within the near future, and the ASSOCIATION, naturally, does not have the funds to take care of this relatively small debt, but is dependent upon those who are interested in the welfare of pharmacy and the ASSOCIATION to provide the money. In addition to this, the ASSOCIATION, if it is to carry out effectively its conservative service plan, needs $12,000.00 to $15,000.00 additional income a year, and this would require several hundred thousand dollars to produce the necessary income.

The service and development plan which has been formulated is one of great value to pharmacy in general, and is not only practical and conservative, but necessary.

I can assure you that the emergency fund of $100,000.00 will be provided in one way or another, but I do hope that all who are interested in pharmacy will indicate their further approval of the work of the AMERICAN PHARMACEUTICAL ASSOCIATION by subscribing whatever may be deemed proper and equitable. A few thousands of dollars will, I am sure, not mean much to the large interests, but will mean a great deal to this most worthy cause, which is in your interest and mine. A few hundreds, or even a few dollars, from a large number of contributors would, in the aggregate, represent a considerable sum.

I want to make clear that, under my guidance, the AMERICAN PHARMACEUTICAL ASSOCIATION has not over-reached itself in the development of this project, as represented by the American Institute of Pharmacy Building. The quarters which have previously been occupied by the ASSOCIATION in Baltimore were entirely inadequate and the work has been carried out under most disadvantageous conditions and, yet, even though a special concession was made in the rent during the depressed times, the rental costs amounted to $1200.00 a year. In the present building all operating expenses, including every cost, are less than $4500.00. This is due to the fact that the building is provided with automatic equipment of every kind, including heating, lighting, telephone, sprinkling system, etc., and, most particularly, that the property is tax free. You will, therefore, understand that these splendid new quarters for the A. PH. A. at present cost only $3300.00 more than the inadequate accommodations which they had here in Baltimore.

The National Association Boards of Pharmacy have voted to place their executive offices in the building during 1935 and will share the expenses to the extent of $1000.00 minimum. This will reduce the difference between the old costs and the new to $2300.00. Other non-profit organizations, such as the executive offices of the American Association of Colleges of Pharmacy, Enforcement Officers, and similar organizations, are seriously considering joining the Boards of Pharmacy organi-

zation in having their executive offices in this building and, in all probability, action will be taken within the near future. This, you will understand, will reduce the overhead costs of the A. PH. A. and of these associated organizations to a very reasonable basis and make the costs of operating in this fine building no greater, and perhaps less, than was formerly the case.

The development of the museum and library is already progressing and will come through special contributions and donations. So we need not worry about these two departments.

The income from the membership dues of the A. PH. A. just about pays operating expenses for the services given to the members of the ASSOCIATION. There are special endowment funds which can be used for special purposes.

The real reason for a maintenance fund is to give the opportunity to the A. PH. A. to employ one or more outstanding pharmacists, having the crusader spirit, who will go into the building with the idea of developing educational propaganda and service features in the way of pamphlets, lectures, etc., which will aid in the regeneration of the practice of pharmacy.

The immediate object of the A. PH. A. and the service work in the Institute is to regenerate pharmacy through the education of the pharmacists and the stimulation of the public to demand a better professional service. This can be accomplished by taking drugs out of the merchandising stores and establishing pharmacies which will sell drugs, sick-room requisites and accessories, but excluding the kind of merchandise which has no direct relationship to pharmaceutical practice. This can, will and must be accomplished, because the public will demand it when it realizes the dangers of having inexperienced men dispensing drugs which are, in a large measure, poisons, and requires special knowledge and experience. This regeneration will not happen immediately, because the public does not realize, as yet the full danger.

I am convinced that, as long as drugs are used in the practice of medicine and for the cure of disease, the practice of pharmacy will be important, and I am equally confident that the public will realize it when the bad practice of pharmacy results in serious consequences, inclusive of accidental deaths, due to carelessness and inefficiency. It is true that the pharmacist is better educated than ever before, but he has less opportunity to make use of his education; eventually he will, and that is the A. PH. A.'s immediate job, to see that the pharmacist is provided with an opportunity to use the knowledge and information which he obtains in the schools. I know you realize, as well as I do, that it would be a great loss to manufacturing pharmacy if we were obliged to distribute through merchandising stores having no professional aspects or prestige with the public.

I have discussed the real purpose and plans of the A. PH. A. as I see them, and can assure you that it is not attempting too large a program, not even a large program, and that it cannot fail and will not, but it can be seriously handicapped by having insufficient funds which could be so readily furnished by those who are interested in pharmacy and who would benefit greatly. I am not a dreamer or an idealist, and I have never wasted money and do not intend to do so in this instance.

Now, to explain the proposed research development. This really represents an entirely separate proposition, in a sense. An interested member has under consideration offering the first unit, of conservative size and practical value, of a build-

ing for research, immediately adjoining the present institute and in the rear of it. This unit would probably cost $150,000.00 or more, but the plan involves the complete endowment of the undertaking, including the erection of the building, equipment, operating expenses and a fund to pay a limited number of research workers, entirely without cost to the ASSOCIATION. The offer will not be accepted on any other basis. You will understand that the research building will be no burden whatsoever on the ASSOCIATION, but will provide an opportunity for our workers on National Formulary and U. S. P. problems, in coöperation with the voluntary work of the research divisions of the large manufacturing pharmaceutical houses. I know you recognize that, although much of this investigative work is accomplished by individual voluntary workers and institutions, including the different drug institutions, it does and will require several investigators to confirm the tests, correlate the work and reach final conclusions.

You, of course, know that the Food and Drug Division is demanding more and better service from the committees on the Pharmacopœia and National Formulary. If they do not get the required standards from the present sources, they will, I fear, adopt their own standards, and this very important function of the Pharmacopœia and National Formulary may be lost to pharmacy, which would be a great catastrophe to pharmacy and the public. There is quite a lot of necessary work that can be done in this laboratory building, if it is established, and, if not, in the small laboratory in the present building, which would be of great value to pharmaceutical practice, to the Food and Drug Division and to other divisions of the government. The testing and standardizing of the vitamin content of cod liver oil and the distribution of standard samples of pharmaceutical manufacturers is a type of service that can be expected. There is no doubt in my mind that the A. PH. A. can be a great force in promoting satisfactory relationships between pharmacy, the Food and Drug Division and the various public health services which exist in Washington.

I hope that all those interested in the practice of pharmacy and its importance to all phases of pharmaceutical endeavor and the public, will visit the American Institute of Pharmacy Building and take the opportunity to confer with Dr. E. F. Kelly and others before making a final decision in regard to upholding the hands of the AMERICAN PHARMACEUTICAL ASSOCIATION by subscribing to the fund which is required to pay off the small indebtedness and establish a reasonable maintenance fund. The subscription can be whatever amount might be considered proper, and any amount would be helpful—$25.00, $50.00, $100.00, $500.00, $1000.00. The whole amount may be paid in instalments over a period of five years. A $25.00 subscription would represent $5.00 a year for five years; a $50.00 subscription would represent $10.00 a year for five years; a $100.00 subscription would represent $20.00 a year for five years; a $500.00 subscription would represent $25.00 each quarter for five years; a $1000.00 subscription would represent $50.00 a quarter for five years.

Exclusive of my own donation, there has been subscribed, thus far, $61,250.00.—H. A. B. DUNNING, *Chairman, Maintenance Fund Committee.*

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins, George D. Beal, L. W. Rising, H. M. Burlage, L. W. Rowe, John C. Krantz, Jr., Heber W. Youngken.

THE ACTION OF ERGOT AND ITS ALKALOIDS ON THE PUERPERAL UTERI OF DOGS.*[1]

BY EDWARD E. SWANSON AND CHESTER C. HARGREAVES.

Since the isolation of the alkaloids, ergotoxine by Carr and Barger (1) in 1906 and ergotamine by Stoll (2), (3), (4) in 1920, the subject of ergot has been the source of considerable investigation. Of distinct interest is the more recent work of Moir (5), who has shown clinically that ergotoxine is just as effective as ergotamine. Moir (6) in the continuation of his clinical study, observed an effect with the fluidextract, when given by mouth, that has a much more rapid onset of action on the puerperal uterus than either ergotoxine or ergotamine.

In our comparative pharmacological study of the fluidextract of ergot and its active principles by the various well-known methods the intact puerperal uterus of dogs has been helpful as a method of test.

This method is based on the use of intact dog uteri, three to six days post-partum. Under ether anesthesia, an elongated rubber balloon or bag (five inches long and one and one-half inches in diameter) is inserted through the vagina into either the right or left fallopian tube. For definite location of the balloon in the uterine horn, an abdominal incision is made. The balloon is attached to a tambour by a rubber tube. Before each experiment this closed system is tested for leaks.

In these experiments more than a hundred dogs were used. The drugs were given by vein and by mouth in doses distinctly larger than that used by Moir (5), (6).

Clinically, Moir (5) has shown that ergotoxine or ergotamine in doses of 1 mg. to 3 mg. by mouth produces slow and erratic results on the uterus. The onset of action is delayed for thirty-five minutes to one hour or more. For the fluidextract or liquid extract B. P. 1914 given orally in doses of 2 to 4 drachms, Moir (6) observed that the onset of action on the uterus is strikingly shorter than that of the alkaloids.

As shown in Table I, by the U. S. P. Cock's Comb and Reversal Uteri Methods the various preparations, with the exception of the liquid extract of ergot B. P., have approximately the same potency.

By vein, as shown in Table II, the onset of action is approximately the same for the fluidextract, liquid extract B. P. 1914, ammonia extract, acetone extract, ether extract, ethylene dichloride extract, sulphur dioxide extract and alkaloids ergotoxine or ergotamine. With doses of 0.2 cc. per Kg. of the fluidextract U. S. P., the liquid extract B. P. 1914, 0.1 mg. of the various extracts or 0.1 mg. per Kg. of the alkaloids, the onset of action on the uterus is one to one and one-half minutes.

* Scientific Section, A. PH. A., Madison meeting, 1933.

[1] This paper was passed by the Board of Review on Papers and returned to the authors for addition of kymographic tracings.—*Editor*.

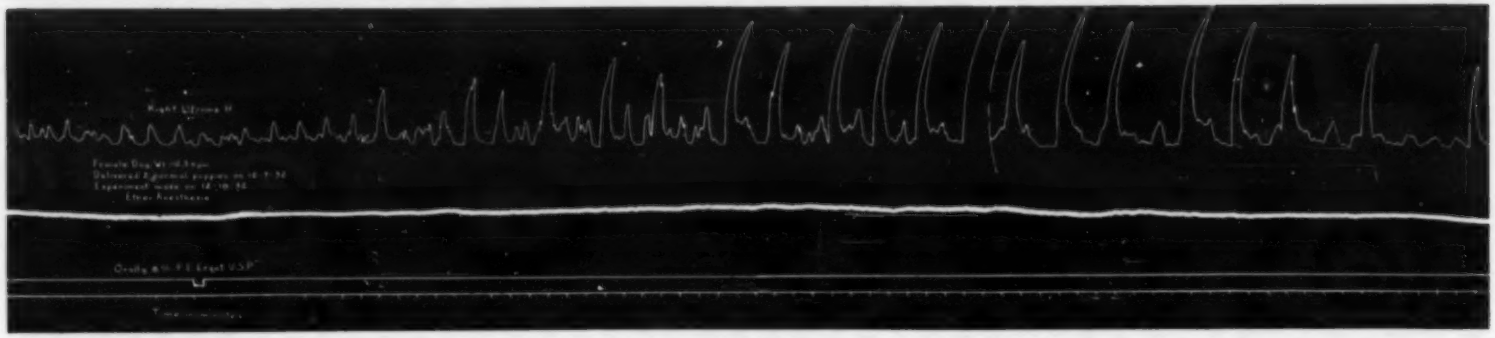

Fig. 1.—Represents an etherized dog with recorded puerperal uterine contractions. Fluidextract ergot U. S. P., 0.65 cc. per Kg. was given by mouth. In ten minutes the uterus began to show increase in contractions. These contractions increased in amplitude and remained strong for more than sixty minutes.

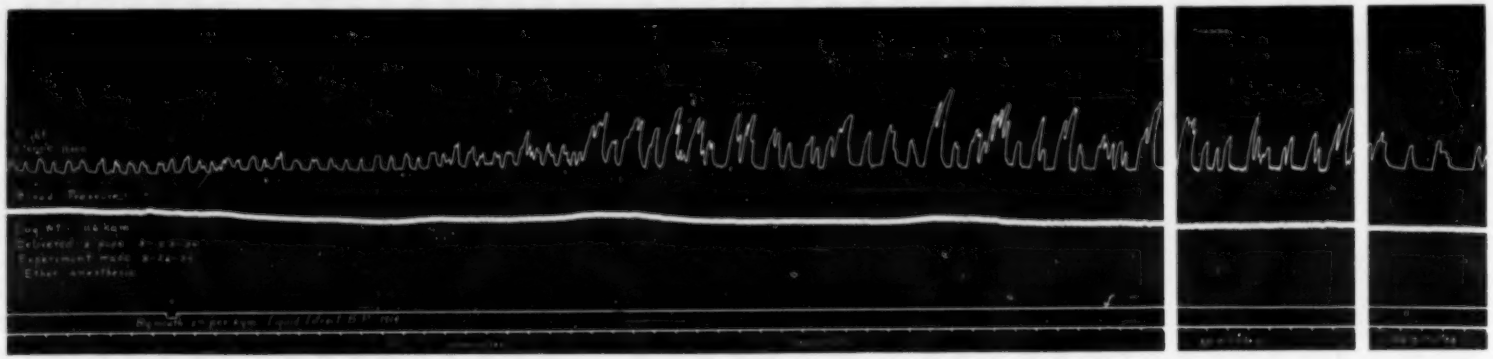

Fig. 2.—An etherized dog with recorded blood pressure and puerperal uterine contractions. Liquid extract of ergot B. P. 1914, 2 cc. per Kg. was given by mouth. In fourteen minutes the contractions of the uterus began to show stimulation. The contractions were strong for more than one hundred minutes.

Thus, by vein, the time of onset of action for the alkaloids is the same as that of the fluidextract of ergot U. S. P., the liquid extract of ergot B. P. 1914 or the various extracts.

By mouth as shown in Table III, the onset of action of the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914, various extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide) is more rapid than that of the alkaloids ergotamine or ergotoxine. With a standard fluidextract of ergot U. S. P. in doses of 0.2 cc. to 1 cc. per Kg. (equivalent to 0.1 mg. to 0.5 mg. per Kg. of the alkaloids) the onset of definite response is eight to twenty

TABLE I.

Preparation.	U. S. P. Cock's Comb Method.	Reversal Uteri Method.
Fluidextract Ergot U. S. P.	100%	100%
Liquid Extract of Ergot B. P. 1914	25%	40% to 50%
Ammonia Extract of Ergot	100%	90%
Acetone Extract of Ergot	...	100%
Ether Extract of Ergot	...	90%
Ethylene Dichloride Extract of Ergot*	110%	112%
Sulphur Dioxide Extract of Ergot*	100%	80%
Ergotamine Tartrate Sandoz	100%	100%
Ergotoxine Ethanesulphonate	110%	120% to 130%

* Process patent applied for.

TABLE II.—PUERPERAL UTERI OF DOGS, INTRAVENOUS ADMINISTRATION.

Dog No.	Body Weight, Kg.	Number of Days, Post-partum.	Drug.	Dose in Cc. or Mg. per Kg.	Time of Onset of Definite Response, Minutes.	Duration of Action, Minutes.	Remarks, Contractions.
1	8.5	5	Fluidextract of Ergot U. S. P.	0.2 cc.	1.5	40	Strong
2	15.0	4	Liquid Extract of Ergot B. P. 1914	0.2 cc.	1.0	25	Strong
3	9.8	4	Ergotoxine	0.2 mg.	1.0	30	Strong
4	8.9	5	Ergotamine	0.1 mg.	1.5	35	Strong
5	16.5	4	Ammonia Extract of Ergot	0.1 mg.	1.0	50	Very strong
6	15.0	3	Acetone Extract of Ergot	0.1 mg.	1.5	15	Fair
7	13.5	4	Ether Extract of Ergot	0.1 mg.	1.5	25	Fair
8	17.0	4	Ethylene Dichloride Extract of Ergot	0.1 mg.	2.0	30	Strong
9	9.2	3	Sulphur Dioxide Extract of Ergot	0.1 mg.	1.0	50	Very strong

minutes. In doses of 2 cc. per Kg. (equivalent to 0.5 mg. per Kg. of ergotamine as determined by the Reversal Uteri Method or the U. S. P. Cock's Comb Method) the time of onset of action with the liquid extract B. P. 1914 is about ten to twenty minutes. As shown in Table III, the various extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide) in doses of 0.1 mg. to 1 mg. per Kg. (equivalent to ergotamine as determined by the Reversal Uteri and U. S. P.

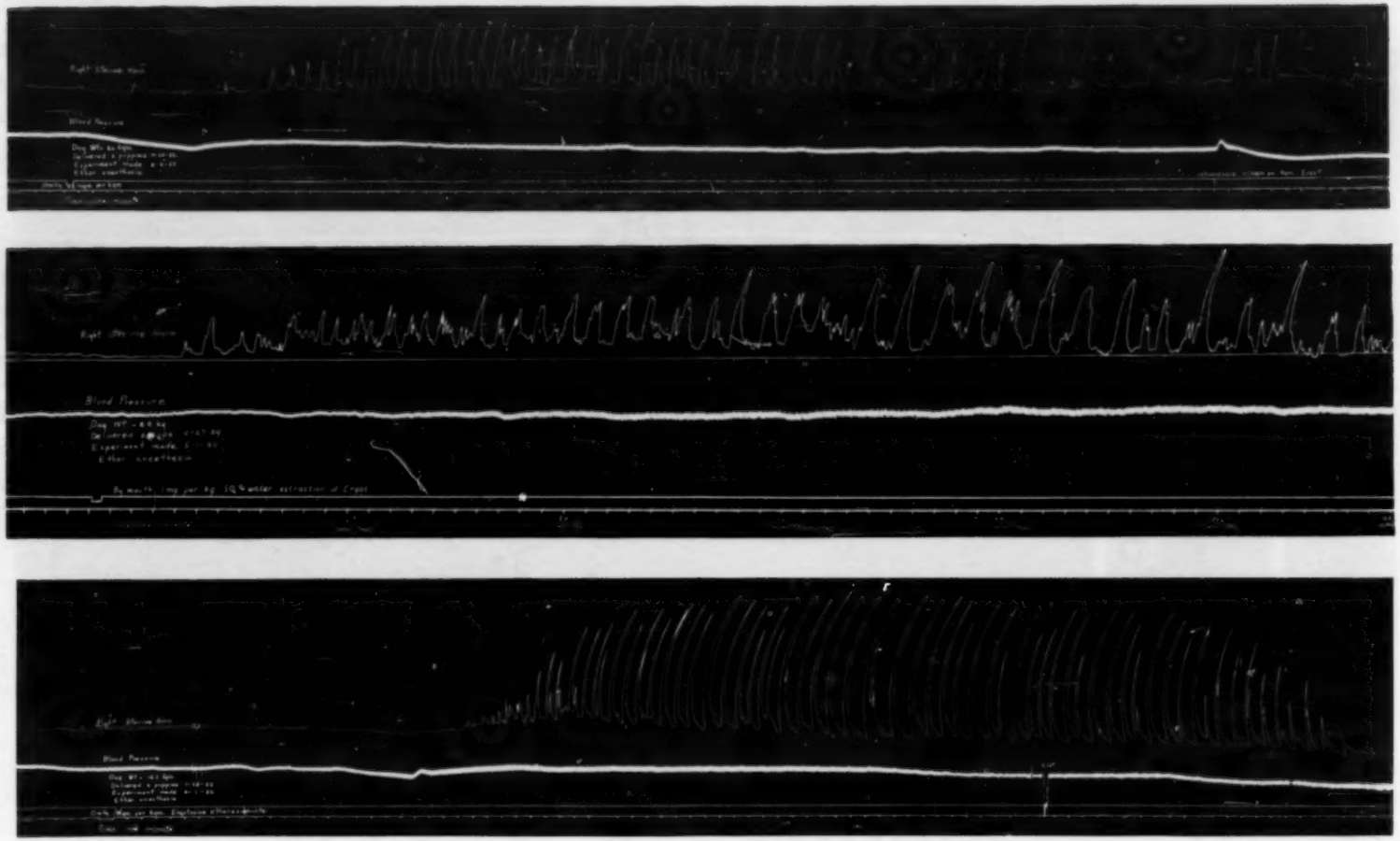

Fig. 3.—Represents a dose of 0.2 mg. per Kg. of the ammonia extract by mouth. There was definite response of contraction of uterus in thirteen minutes. Fig. 4.—Represents an etherized postpartum dog with uterine contractions. The sulphur dioxide extract by mouth produced definite response of contraction of uterus in five minutes. Fig. 5.—An etherized dog with recorded blood pressure and puerperal uterine action. Ergotoxine ethanesulphonate 1 mg. per Kg. was given by mouth. In thirty minutes the contractions of the uterus began to show effects of the ergot. The contractions were very strong for more than sixty minutes.

Cock's Comb Methods) produce definite response of action by mouth in four minutes to fifteen minutes. Thus, by mouth, the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914, or the various extracts of ergot as shown in Table III, have approximately the same time of onset of action on the puerperal uteri of dogs.

As shown in Table III, with ergotamine in doses of 0.4 mg. to 1 mg. per Kg. the time of definite response is forty to fifty minutes. In doses of 0.5 mg. to 1 mg. per Kg. with ergotoxine definite action is shown in thirty to sixty minutes. Thus, both ergotamine or ergotoxine have a more prolonged definite onset of response on the puerperal uteri of dogs than that of the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914 or the extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide).

TABLE III.—PUERPERAL UTERI OF DOGS, ORAL ADMINISTRATION.

Number of Dog.	Body Weight, Kg.	Number of Days, Post-partum.	Drug.	Dose in Cc. or Mg. per Kg. Cc.	Time of Onset of Doubtful Response, Minutes.	Time of Onset of Definite Response, Minutes.	Duration of Action, Minutes.	Remarks, Contractions.
10	19.4	4	Fluidextract Ergot U. S. P.	0.2	..	8	40	Weak
11	7.1	3		0.5	..	12	30	Strong
12	12.3	3		0.65	5	10	90	Powerful
13	14.1	6		0.70	4	20	40	Strong
14	8.0	5		1.00	4	8	60	Strong
15	12.0	4		1.00	10	15	70	Strong
16	11.9	4		1.00	..	10	50	Strong
17	14.8	4		1.00	6	12	100	Strong
18	10.0	4	Liquid Extract of Ergot B. P. 1914	1.00	None	None	None	No response
19	24.0	3		2.00	..	10	60	Strong
20	11.6	3		2.00	10	14	120	Strong
21	8.4	4		2.00	10	20	50	Strong
22	15.0	4		2.00	9	16	40	Strong
23	16.8	3	Ergotamine Tartrate	0.10	None	None	None	No response
24	11.0	5		0.20	None	None	None	No response
25	11.0	4		0.20	..	50	30	Weak
26	5.0	4		0.40	..	40	50	Weak
27	8.0	3		0.50	..	60	40	Weak
28	8.1	3		0.60	..	45	70	Strong
29	8.1	4		1.00	10	48	60	Strong
30	10.0	5		1.00	..	55	50	Strong
31	12.7	3	Ergotoxine Ethanesulphonate	0.20	None	None	None	No response
32	3.9	6		0.50	..	40	30	Weak
33	11.7	5		0.50	..	60	30	Weak
34	12.5	4		0.50	..	50	30	Strong
35	18.4	6		1.00	25	30	60	Powerful
36	8.2	5		1.00	..	40	30	Strong
37	10.2	4		1.00	..	30	40	Strong
38	13.0	3		1.00	..	50	50	Strong
39	22.4	4		1.00	..	40	120	Powerful
40	14.6	4		0.07	None	None	None	No action
41	13.4	5		0.08	None	None	None	No action
42	14.0	4		0.10	..	4	30	Weak
43	10.5	4		0.10	..	8	40	Strong

Fig. 5.—An etherized dog with recorded blood pressure and puerperal uterine action. Ergotoxine ethanesulphonate 1 mg. per Kg. was given by mouth. In thirty minutes the contractions of the uterus began to show effects of the ergot. The contractions were very strong for more than sixty minutes.

TABLE II.—*Continued.*

44	12.6	5		0.15	None	None	None	Leak in system
45	15.6	4	Ammonia Extract of Ergot	0.20		5	40	Strong
46	15.2	4		0.20	None	None	None	Leak in system
47	8.6	4		0.20	10	13	60	Strong
48	8.6	3		0.25	..	10	30	Strong
49	14.2	4		0.50	..	8	50	Powerful
50	16.5	5		0.50	..	10	50	Powerful
51	9.5	4		0.60	5	15	60	Powerful
52	13.5	4		1.00	..	9	30	Powerful
53	14.0	4	Acetone Extract of Ergot	1.00	5	10	35	Fair
54	11.5	3	Ether Extract of Ergot	1.00	8	13	45	Fair
55	10.0	3	Ethylene Dichloride Extract of Ergot	1.00	10	14	40	Strong
56	13.0	4		1.00	10	12	30	Fair
57	8.7	3		1.00	9	15	120+	Powerful
58	10.6	3	Sulphur Dioxide Extract of Ergot	1.00	3	4	30	Strong
59	12.4	3		1.00	3	4	40	Strong
60	8.9	4		1.00	3	5	60+	Powerful

CONCLUSIONS.

1. As a pharmacological method the intact puerperal uteri of dogs is helpful in the study of the active principles of ergot.

2. On the puerperal uterus the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914 and the various extracts by mouth show a more rapid onset of definite contractions than that of the alkaloids, ergotamine or ergotoxine.

3. Ergot contains a principle (not ergotamine or ergotoxine) that produces by mouth a rapid onset of action on the puerperal uterus of dogs.

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(2) A. Stoll, "Zur Kenntnis der Mutterkornalkaloid," *Verhandl. Schweiz. Naturl. Gesellsch.* (1920), 190.

(3) K. Spiro and A. Stoll, "Ueber die wirksamen Substanzen des Mutterkorns," *Schweiz. med. Wochschr.*, 2 (1921), 525.

(4) A. Stoll, "Über Mutterkorn," *Schweiz. Apoth.-Ztg.*, Nos. 26–28 (1922).

(5) C. Moir, "Clinical Comparison of Ergotoxine and Ergotamine," *Brit. Med. J.*, 1 (1932), 1022.

(6) C. Moir, "The Action of Ergot Preparations on the Puerperal Uterus," *Ibid.*, 1 (1932), 1119.

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DIGITALIS GLYCOSIDES. E. Leger. (*J. pharm. chim., Paris*, 18 (1933), 482.) This review of the work of many authors upon the digitalis glycosides shows that although these glycosides differ, especially with respect to the number and nature of the sugar molecules with which the aglycones are associated, there is a close relationship between the aglycones themselves. The knowledge of the constitution of one of these aglycones would furnish the key to the constitution of the remainder.—G. M. MELHUISH in *Quarterly Journal of Pharmacy and Pharmacology*, 7 (1934), 127.

PRELIMINARY REPORT UPON CHEMICAL EXAMINATION OF THE ENTIRE PLANT OF CELASTRUS SCANDENS.*

BY NELLIE WAKEMAN.

(WITH CARL BUHLER, HARVEY KIMBEL, ALBERT NIEBAUR, ANDREW RUZEK AND VINCENT WASZ.)

The entire plant was collected in the fall and separated into leaves, fruit, bark, wood and root, each of the five students being given a part for investigation. The work, though still in the preliminary stages, has yielded extremely interesting products.

The general plan followed in this examination was to dry the plant material, reduce it to powder, and then extract it by continuous percolation with petroleum ether, ether and alcohol successively. Moisture determinations of both fresh and dried material, and ash determinations, were made of each plant part.

Leaves.—The dried and powdered leaves had a beautiful bright green color. Both the petroleum ether and the ether extracts from this powder were rich in chlorophyll. From these extracts a thick dark oily product resulted. Its saponification value is low. From it there has been obtained an unsaponifiable residue which is precipitated by digitonin and responds to the color reactions for sterols.

From the alcoholic extract of the leaves there has been isolated a small quantity of a white crystalline substance which has a sweetish taste but does not reduce Fehling's solution. Upon hydrolysis, however, it has reducing properties. This material is difficultly soluble in cold alcohol, much more soluble in hot alcohol, soluble in dilute alcohol, especially when hot, and in water.

Stem.—The bark of the stems was tough and stringy when dried. It could not be ground in a mill, so it was clipped with scissors into pieces about an eighth of an inch long, packed in a percolator and extracted in the same way as the leaves. The extracts were somewhat greenish in color though little chlorophyll was extracted. As from the leaves, an unsaponifiable substance which responded positively to tests for sterols was obtained, also the same, or a similar, white crystalline substance. This melted at 182°. Upon hydrolysis no evidence of a non-sugar material was found. The hydrolyzed product reduced Fehling's solution and yielded, with phenylhydrazine, an osazone which melted at 190–191° and resembled, in its crystalline form, galactosazone.

The wood of the stem also yielded a sterol-like substance and a white crystalline product which was, at first, thought to be identical with that from the leaves and bark, but which refused to hydrolyze and yield a reducing sugar. This material resembles in appearance, taste and solubility the hexatomic alcohols, mannitol, dulcitol, sorbitol. Its melting point, by repeated crystallizations, was raised to 186°, too high for mannitol or sorbitol but approaching that of dulcitol.

Root.—The red outer bark of the root was carefully removed with a knife, then ground to powder. This powder was packed in a percolator and extracted by continuous percolation with low boiling petroleum ether (Skellysolv B, b. p. 65°). After extracting for about three hours the heat was removed, and the deep red

* Scientific Section, A. PH. A., Washington meeting, 1934.

petroleum ether extract was allowed to stand over night. In the morning beautiful ruby red crystals were found to have separated in the flask. These were filtered on a pad of solid carbon dioxide and kept in a sealed tube filled with the gas. They melt at 192°, the melting point of β-carotene, and resemble β-carotene in solubility and crystalline form. Longer extraction with petroleum ether produced more of the red product and, finally, an orange-colored powdery precipitate, which is easily separated from the red crystals by washing with ether.

Work upon the woody portion of the root has scarcely begun. There is being obtained, however, a sterol-like substance and a white crystalline substance resembling those from the leaves and stem.

Fruit.—The outer husk was separated from the fruit and it and the berry were dried separately. The dried husks were ground in a mill. The berries, after drying, were rubbed on a coarse sieve with a large cork, and the arillus was thus separated from the seed. The coarse powder thus obtained was of a deep red color. It and the powdered husks were extracted separately with low boiling petroleum ether. From the deep red extracts no crystals separated upon standing. The extracts were then concentrated by distillation of the petroleum ether, and red fatty masses resulted, that from the arillus of the seed being the more intensely colored. This product was saponified by boiling with alcoholic potassium hydroxide. After the alcohol was evaporated water was added to the reaction mixture and it was shaken out with ether. Small deep red needle-shaped crystals separated upon evaporation of the ether. Only a small quantity of this material has been obtained. Neither it nor the other products of the hydrolysis have been investigated.

There have, therefore, been isolated from the plant, and partly identified:

One or more substances which respond to the tests for sterols.

One or more red crystalline substances which resemble carotene, probably β-carotene.

Two or more white crystalline substances, one of which yields upon hydrolysis a reducing sugar which forms an osazone with the melting point and crystalline form of galactosazone. The other is non-sugar in character, probably a sugar alcohol, possibly dulcitol.

All of these products, and others not so well characterized, are undergoing further examination and will be reported upon later.

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SOME OBSERVATIONS ON THE STABILITY OF QUININE SULPHATE DURING STORAGE.*

BY L. E. WARREN.[1]

Under certain conditions quinine sulphate may crystallize from water with 8 molecules of water of hydration. This product rapidly loses some of its water,

* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] Food and Drug Administration, Washington, D. C.

even while drying during the process of manufacture, so that the more usual form contains moisture, equivalent to about 7 or $7^1/_2$ molecules of water. It has been known for many years that quinine sulphate containing more than 2 molecules of water of hydration is unstable. On standing at ordinary temperatures the salt loses water until the equivalent of only about two molecules remain. This change takes place very rapidly at 50° C. After the two-molecule stage has been reached the product remains stable unless subjected to temperatures appreciably higher than those usual in the laboratory or to other unusual treatment, such as storage in a desiccator.

The U. S. Pharmacopœia permits either 7 or 8 molecules of water of hydration. It prescribes a maximum limit for loss on drying (16.2 per cent) which is very nearly the value corresponding to 8 molecules of water of hydration (16.16 per cent). It prescribes no minimum limit for loss on drying. Concerning the instability of the fully hydrated salt the U. S. P. X makes the following statement:

> "It effloresces rapidly when exposed to dry air or when heated to 50° C., losing all but two molecules of its water of crystallization and becoming lusterless."

Although there are several references in the literature to the instability of quinine sulphate during storage, exact information concerning the length of time required (at room temperature) for the crystallized salt to lose sufficient of its water to reach the stable form is inadequate.

In 1876 Cownley[1] observed that freshly prepared quinine sulphate contained $7^1/_2$ molecules of water of crystallization and that it lost $5^1/_2$ of these when freely exposed to the air for 28 hours.

In 1884 Parsons[2] reported that he had determined the water in 1015 samples of quinine sulphate by drying in a water oven. The average water content was 13.849% or slightly above $6^1/_2$ molecules (13.56 %). He suggested that the stable salt with 2 molecules of water of crystallization be introduced in the U. S. P. VII.

In 1886 Spalding[3] reported that he had weighed the contents of two cans of quinine sulphate and repeated the weighings over a period of 12 months in one instance and 8 months in the other. The total loss in the first case amounted to between 8% and 9% and in the second to 11.39%. No information was given as to how long the containers remained open at the time of the weighings.

In 1892 Thompson[4] reported that he had found an average water content of 11.74% in 183 samples of quinine sulphate on the market.

In 1924 Linerseege[5] called attention to this problem in its relation to public analysts in Great Britain. He says in part:

> Owing to some samples of medicine containing an excess of quinine, seven samples of the sulphate were bought from pharmacies. The amount of moisture varied from 3.7 per cent to 12.0 per cent, with an average of 6.4 per cent, not one of them corresponding with the $7^1/_2$ molecules, or 15.3 per cent of water required by the B. P. description. The 1898 B. P. required the freshly

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[1] "The Water of Crystallization in Quinine Sulphate," *Pharm. J. & Trans.* (3), 7 (1876), 189.

[2] "On the Water of Hydration in Quinine Sulphate," PROC. A. PH. A., 32 (1884), 457.

[3] "Sulphate of Quinine—Loss in Weight when Packed in Cans," *Ibid.*, 34 (1886), 605.

[4] "Quinine Sulphate U. S. P.," *Ibid.*, 40 (1892), 266.

[5] "Quinine Sulphate," "Year Book of Pharmacy," 61 (1924), 756.

prepared salt to lose 15.2 per cent of moisture on heating. This test was omitted in the 1914 B. P., and nothing put in its place. Both Pharmacopœias remark under "Characters and Tests" that the crystals effloresce on exposure to dry air until two molecules of water remain. What, therefore, is the amount of moisture in the B. P. salt? Is it $7^1/_2$ molecules, as required by the description, or anything between that and two molecules, as is suggested by the latter statement? This is a difficult question for an analyst who receives samples of quinine sulphate or medicine containing it. The retail samples given above show how variable the salt is, and one wholesale sample contained 3.9 per cent of moisture.

Linerseege suggested that the next revision of the British Pharmacopœia should describe a salt containing but two molecules of water of crystallization. However, the new edition (1930) still describes a salt with $7^1/_2$ molecules of crystallization.

Two one-ounce bottles of quinine sulphate of the same brand were obtained by Sage[1] from the manufacturer. One was opened immediately and small portions were removed from time to time for a period of two years. The other was kept sealed beside the opened bottle. Water was then determined in each. The salt from the frequently opened bottle lost 3.76% on drying and the other 13.28%. The initial moisture content of the salt in the first opened bottle was not stated.

In 1933 Beal and Szalkowski[2] determined loss in weight at 100° on twenty-eight specimens of quinine sulphate, representing market material. A specimen containing 16.78% of H_2O and an anhydrous specimen were prepared. The market material lost from 4.39% to 12.29%, or calculated as H_2O, from 1.9 to 5.8 molecules. None of the market specimens conformed to the U. S. P. which limits the loss at 100° to 16.2%. Portions of both of the prepared specimens were exposed in desiccators 14 days to concentrated sulphuric acid, 3:1 sulphuric acid, 2:1 sulphuric acid, 1:1 sulphuric acid, saturated solution of potassium acetate (20% humidity), saturated solution of calcium chloride (30% humidity), saturated solution of potassium carbonate (40% humidity) and saturated solution of ammonium chloride (80% humidity). No marked changes took place after the ninth day. The dihydrate (4.60% H_2O) is the most stable form. The heptahydrate (14.43%), the octahydrate (16.16%) and the anhydrous salt tend to form the dihydrate. In changing from the heptahydrate to the dihydrate the salt loses its long, flaky crystalline form which results in short needles that have almost the appearance of fine powder. The salt also loses in bulk.

Wales[3] has shown by vapor pressure measurements that two hydrates of quinine sulphate exist. The octahydrate is unstable under exposure to the air and is transformed into the dihydrate. His findings indicated that under ordinary conditions equilibrium with water vapor in the air would be reached somewhere on the sharp break in the vapor pressure curve and that the salt stored in an open container should contain slightly more than 2 moles of water.

Because of the insufficiency of the information in the literature, and because of the bearing which the facts would have on the administration of the food and drugs act it was decided to carry out some tests in the hope of determining how rapidly the salt would lose its water under such conditions as would ordinarily obtain on

[1] "Quinine Sulphate and Its Storage," *Pharm. J.*, 119 (1927), 264.

[2] "Notes on the Water of Crystallization of Quinine Sulphate," Jour. A. Ph. A., 22 (1933), 1219–1225.

[3] *Ibid.*, 23 (1934), 793.

the shelves of drug stores. Accordingly, in November 1932, seven packages of quinine sulphate were purchased directly from the manufacturer with the specifications that the material should all be of the same lot and that it should have been freshly made and packed. The material was contained in six glass bottles with screw caps, each containing 1 ounce, and in one 8-ounce tin with tightly fitting telescopic cover. The salt in the tin package was protected further by being placed in a sack of blue paper.

The following disposition was made of the material:

A 1-ounce package (A) was opened in the Washington Laboratory immediately after delivery and a small portion taken out for water determination,[1] the package being kept open for 15 minutes. This procedure was repeated once each week until the material no longer lost weight, care being taken to keep the package open for exactly 15 minutes each time a portion was taken out for analysis, and to take the sample from the surface of the contents without mixing the remainder. This was assumed to simulate conditions in prescription practice.

The 8-ounce package (B) was given the same treatment as the 1-ounce package above mentioned.

After an interval of 1 month another package (C), which had been kept sealed in the laboratory since purchasing, was opened and a sample taken for water determination, the container being kept open for 15 minutes. This procedure was repeated once each month until the material ceased to lose weight.

After an interval of 3 months a fourth package (D) (still sealed) was opened and a sample removed once each month for water determination, the package being left open for 15 minutes each time that a sample was removed. The process was repeated until the loss became constant.

After an interval of 4 months a fifth package (E) (still sealed) was opened and a sample removed for water determination once each month until the weight became approximately constant.

One of the 1-ounce packages (F) was sent unopened to the Minneapolis Station of the Food and Drug Administration, and another (G) to the Denver Station with the request that they be opened once each week for 8 weeks and kept uncovered for 15 minutes each time. The request was made also that the product be stored in such manner that direct sunlight would not fall on it. As soon as the specimens had been returned they were opened and the treatment accorded the third specimen given each.

Since all of the specimens were of the same lot it was assumed that the initial water content of all of the 1-ounce packages was the same as that of the two specimens which were first assayed.

At the expiration of one year from the time of purchase all of the specimens were reëxamined for loss on drying. Also at the expiration of one year from the time of opening each specimen was again tested for loss on drying.

The results obtained with the specimens which were analyzed weekly are recorded in Table I; those obtained from the analyses on the monthly basis are given in Table II. The monthly results for Specimens A and B are included also in Table II, four weeks being considered as 1 month.

[1] Water was determined by drying at 90° C.

In Table III the principal results are condensed for ready reference.

TABLE I.—WATER CONTENT OF QUININE SULPHATE AFTER STORAGE FOR DIFFERENT PERIODS.

Sample.	Initial Water Content, Per Cent.	Water Content after 1 Week, Per Cent.	Water Content after 2 Weeks, Per cent.	Water Content after 3 Weeks, Per Cent.	Water Content after 4 Weeks, Per Cent.	Water Content after 5 Weeks, Per Cent.	Water Content after 6 Weeks, Per Cent.	Water Content after 7 Weeks, Per Cent.	Water Content after 8 Weeks, Per Cent.	Water Content after 9 Weeks, Per Cent.
A	12.91 12.91 13.18	12.97 12.91	12.58	11.63	8.93	7.77	9.18 8.35	7.94	6.98	6.65
B	13.48 13.44	12.75 12.44	11.27	10.25	9.56	7.86	6.92	5.81	6.40	6.97

Sample.	Initial Water Content, Per Cent.	Water Content after 10 Weeks, Per Cent.	Water Content after 11 Weeks, Per Cent.	Water Content after 12 Weeks, Per Cent.	Water Content after 13 Weeks, Per Cent.	Water Content after 14 Weeks, Per Cent.	Water Content after 15 Weeks, Per Cent.	Water Content after 16 Weeks, Per Cent.	Water Content after 7 Mos. Per Cent.
A	12.91 12.91 13.18	5.57	5.27	4.63	No assay	No assay	No assay	No assay	No assay
B	13.48 13.44	6.83	5.41	5.37	5.03	5.06	4.84	5.00	4.50

TABLE II.—WATER CONTENT OF QUININE SULPHATE AFTER STORAGE FOR DIFFERENT PERIODS.

Sample.	Initial Water Content, Per Cent.	Water Content after 1 Mo. Per Cent.	Water Content after 2 Mos. Per Cent.	Water Content after 3 Mos. Per Cent.	Water Content after 4 Mos., Per Cent.	Water Content after 5 Mos., Per Cent.	Water Content after 6 Mos., Per Cent.	Water Content after 7 Mos., Per Cent.	Water Content after 8 Mos., Per Cent.
A	12.91 12.91 13.18	8.93*	6.98*	4.63*	No assay	4.56	No assay	No assay	No assay
B	13.48 13.44	9.56*	6.40*	5.37*	5.00*	4.86	No assay	4.50	No assay
C		13.53** 13.00	12.65 11.84	8.70 8.45	6.95	4.56	4.68	4.62	No assay
D				12.09** 11.88	10.33	8.51	7.78	7.36	6.80
E					11.25** 11.21	9.78	8.95	8.56	7.4
F			12.10** 12.09	11.54 11.53	10.42	9.38	8.07	6.84	6.58
G			13.27** 11.25	9.13 9.06	8.78 8.20	9.51	7.94	6.99	No assay

Sample.	Initial Water Content, Per Cent.	Water Content after 9 Mos., Per Cent.	Water Content after 10 Mos., Per Cent.	Water Content after 11 Mos., Per Cent.	Water Content after 12 Mos., Per Cent.	Theory for $Q_2SO_4.2H_2O$, Per Cent.
A	12.91 12.91 13.18	No assay	No assay	No assay	4.84	4.60
B	13.48 13.44	No assay	No assay	No assay	4.51	4.60
C		No assay	No assay	No assay	4.67	4.60
D		7.21	6.37	5.64	4.66	4.60
E		7.81	5.25	4.65	4.84	4.60
F		6.90	No assay	6.60	4.61	4.60
G		No assay	No assay	6.17	4.87	4.60

* Four weeks was considered as a month in these assays.
** Initial assay.

The results in Table I show that Specimen A became stable in 12 weeks and Specimen B in 7 months. The stable stage was reached when the product contained approximately 4.60 per cent of water, or two molecules. Specimen C contained 13.27 per cent of water after storage for one month unopened. It became stable in 4 months after opening, or 5 months after purchase. Specimen D contained 11.98 per cent of water after storage unopened for 3 months. It became stable in 9 months after opening, or 12 months after beginning storage. Specimen E contained 11.23 per cent of water on first opening 4 months after purchase. It became stable in 7 months after opening or 11 months after purchase. The specimens which were not opened until 1, 3 or 4 months after purchase contained nearly

as much water (initial analysis) as the specimens opened and assayed immediately after purchase. The specimen which had been opened weekly in Minneapolis for 8 weeks (but not analyzed there) (F) contained 12.1 per cent of water after its return to the Washington laboratory, or nearly 6 molecules. After monthly opening and sampling in Washington it became stable in 10 months after opening, or 1 year after purchase. Likewise, the specimen which had been opened in Denver (G) contained 12.26 per cent of water (or nearly 6 molecules) after its return to Washington. It became stable in 12 months after opening or 14 months after purchase.

TABLE III.—WATER CONTENT OF QUININE SULPHATE AFTER STORAGE FOR DIFFERENT PERIODS.

Sample.	Treatment before Initial Analysis, Per Cent.	Water Content Initial Analysis, Per Cent.	Water Content 1 Mo. after Opening, Per Cent.	Water Content 2 Mos. after Opening, Per Cent.	Water Content 4 Mos. after Opening, Per Cent.	Water Content 6 Mos. after Opening, Per Cent.	Water Content 8 Mos. after Opening, Per Cent.	Water Content 12 Mos. after Opening, Per Cent.
A	Opened immediately	12.91 12.91 13.18	8.93	6.98	No assay	No assay	No assay	4.84
B	Opened immediately	13.48 13.44	9.56	6.40	5.00	No assay	No assay	4.51
C	Stored 1 month after purchase	13.53 13.00	12.65 11.84	8.70 8.45	4.56	4.62	No assay	4.67
D	Stored 3 months after purchase	12.09 11.88	10.33	8.51	7.36	7.21	6.80	4.86
E	Stored 4 months after purchase	11.25 11.21	9.78	8.95	7.44	7.44	5.25	4.58
F	Opened weekly for 2 mos. but no samples taken, then opened monthly for analysis	12.10 12.09	11.54 11.53	10.42	8.07	6.58	No assay	4.74
G	Opened weekly for 2 mos. but no samples taken, then opened monthly for analysis	13.27 11.25	9.13 9.06	8.78 8.20	7.94	No assay	No assay	4.81

These experiments show that during storage in a climate comparable to Washington, D. C., crystallized quinine sulphate progressively loses water of crystallization until it contains about 2 molecules (4.60%) after which it remains practically stable. The more frequently the specimen is opened the more rapid is the loss. Specimens which are opened occasionally but which are not otherwise disturbed, such as the packages sent to Minneapolis and Denver, do not lose their water of crystallization very rapidly. The conditions under which Specimens A and B were kept probably represent those obtaining in drug store practice more nearly than is the case with the other specimens.

THE HYDRATION OF EMETINE HYDROCHLORIDE AND CODEINE PHOSPHATE.*

BY H. WALES.[1]

I. Emetine Hydrochloride.—The statement in the tenth edition of the United States Pharmacopœia that emetine hydrochloride "contains variable amounts of water of crystallization" is the obvious conclusion to be drawn from the reports of those who have published data on this product.

Paul and Crownley (1) state that considerable difficulty was encountered in obtaining the salt in a state fit for analysis on account of the large quantity of

* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] Drug Control, Food and Drug Administration.

mother liquor retained by the crystals, and decide that it contains six molecules of water of crystallization. Hesse (2) states that emetine hydrochloride crystallizes from water with eight molecules of water of crystallization; that four molecules are easily given up on exposure to the air, and that the anhydrous salt will readily take up $4H_2O$ on exposure to the air. He computes the data given by Frerichs and de Fuentis Tapis (3) as showing $4H_2O$ for a commercial sample and $8H_2O$ for one which they obtained by adding ether to an alcoholic solution of the salt. Hesse states also that Keller (4) found nearly $4H_2O$ in a commercial sample and $3H_2O$ in one which was obtained by adding ether to an alcoholic solution. Carr and Pyman (5) state that emetine hydrochloride recrystallized from water and "dried in air until of practically constant weight retains $7H_2O$." They claim that when recrystallized from methyl alcohol it contains $3^1/_2H_2O$. As indicated by Table I the same lack of consistency is shown in the standards provided by the various pharmacopœias for the water content of emetine hydrochloride. However, only three of these pharmacopœias venture to ascribe a definite hydrate to the product. The British and Brazilian Pharmacopœias state that it contains $7H_2O$ and the Swiss Pharmacopœia that it contains "about $4H_2O$." Incidentally the formula of $C_{30}H_{44}O_4N_2.2HCl$ given in the Pharmacopœias of the United States and Brazil is not as well authenticated as that of $C_{29}H_{40}O_4N_2.2HCl$ which is used by Netherlands, Great Britian, Switzerland and Denmark (5), (7).

TABLE I.—MOISTURE STANDARDS FOR EMETINE HYDROCHLORIDE.

	Min.	Max.
Pharmacopœia of Japan (1919)	..	15%
United States Pharmacopœia (1925)	..	19%
Deutsches Arzneibuch (1926)	..	10%
Nederlandsche Pharmacopee (1926)	10%	14%
Pharmacopœia Brazil (1929)	..	19%
British Pharmacopœia (1932)	15%	19%
Pharmacopœia Helvetica (1933)	10%	13%
Pharmacopœia Danica (1933)	..	15%

Coormans (6) calls attention to the variation in water content of emetine hydrochloride as provided by the different European pharmacopœias and finds that samples manufactured in different countries meet the pharmacopœial requirements of the country of manufacture. The actual amount of water found in the samples of emetine hydrochloride examined by the several investigators is shown in the following table.

TABLE II.—WATER CONTENT OF EMETINE HYDROCHLORIDE.

	Per Cent.	Moles.
Paul and Crownley	19.59	7.5
Frerichs and de Fuentis Tapis	12.57	4.4
	19.51	7.4
Keller	10.16	3.5
	8.31	2.8
Hesse	19.91	8.2
	12.73	4.5
	12.54	4.4

TABLE III.—VAPOR PRESSURE AT 25° C. OF EMETINE HYDROCHLORIDE CONTAINING VARYING AMOUNTS OF WATER.

Water in Sample, Per Cent.	Moles Water in Sample.	Vapor Pressure in Mm.
28.14	12.0	23.0
26.84	11.3	22.1
25.62	10.8	21.8
24.29	9.9	20.0
22.04	9.1	18.4
19.93	7.6	16.0
18.65	7.0	14.5
17.56	6.6	13.1
16.37	6.0	11.5

TABLE II.—*Continued.*

Carr and Pyman	17.4	6.5
	19.0	7.3
	18.2	6.9
	18.4	7.0
	17.3	6.5
	19.2	7.3
Coormans	16.34	6.0
	13.0	4.6
	15.0	5.4
	13.9	5.0
	10.25	3.5
	9.5	3.2

TABLE III.—*Continued.*

15.24	5.5	10.0
12.69	4.5	7.0
10.62	3.7	4.6
8.51	2.8	3.3
6.97	2.3	2.5
4.90	1.6	1.2
3.19	1.0	0.8
0.83	0.3	0.2

The vapor pressure of emetine hydrochloride, progressively dehydrated at 25° C., was determined by the method already described for quinine sulphate (8). As can be readily seen from the accompanying table and curve no evidence of a hydrate is shown. The vapor pressure of the solution of water in emetine hydrochloride is so low that the product will be in equilibrium with atmospheric conditions when it contains between 8% and 16% of water. This water is, however, merely adsorbed or dissolved in the emetine hydrochloride. It does not exist in the form of a hydrate.

II. Codeine Phosphate.—Codeine phosphate is described in the British Pharmacopœia (1932) as containing one molecule of water of crystallization. The German (1926), Swiss (1933) and Danish (1933) Pharmacopœias state that it contains one and one-half molecules of water while the United States (1926), Swedish (1925), French (1925) and Brazilian (1929) Pharmacopœias ascribe two molecules of water of crystallization to the product.

Anderson (9) reports that codeine phosphate crystallized from water contains approximately $1^1/_2H_2O$. Schmidt (10) states that when crystallized from water it contains $2H_2O$ and from dilute alcohol $^1/_2H_2O$. Beilstein (11) and Tambach and Henke (14) both give the formula with $1^1/_2H_2O$. Schaefer (12) states that "all the preparations on the market contain only $^1/_2$ molecule of water of crystallization. The salt with 2 molecules of water exists but it is a practical impossibility to produce it for commercial purposes." Henry (13) states that codeine phosphate contains 1, $1^1/_2$ or $2H_2O$.

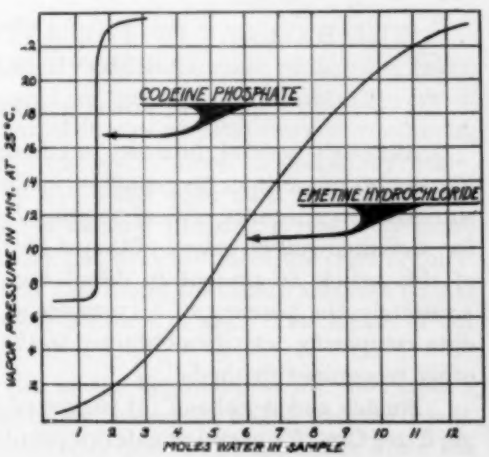

Fig. 1.

Codeine phosphate progressively dehydrated at 25° C. by the method described above gave the following results.

As will be seen from the accompanying curve codeine phosphate crystallized

from water at room temperature contains one and one-half molecules of water of crystallization. No evidence of any other hydrate is indicated by these results.

TABLE IV.

Per Cent Water in Sample.	Moles Water in Sample.	Vapor Pressure in Mm.	Per Cent Water in Sample.	Moles Water in Sample.	Vapor Pressure in Mm.
8.15	1.96	23.0	4.56	1.05	7.0
7.61	1.82	21.0	3.71	0.85	7.0
6.80	1.61	18.0	3.20	0.73	6.6
6.57	1.55	9.0	2.96	0.67	7.0
6.22	1.47	7.5	2.07	0.47	6.5
6.06	1.42	7.1	1.49	0.33	6.0
5.53	1.24	7.0	1.18	0.26	5.0
4.84	1.12	7.0			

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THE BIOASSAY OF THE ANTERIOR PITUITARY-LIKE SEX HORMONE (ANTUITRIN S).*

BY L. W. ROWE, A. SIMOND AND W. O. NELSON.

Although several bioassay methods for evaluating the anterior pituitary-like sex hormone from pregnancy urine have been suggested, none of them has been subjected to adequate critical scrutiny for accuracy nor has there been much basis for a comparison of values obtained by different methods. It will be the purpose of this article to present in detail the method which has been used to control accurately the potency of a commercial product (Antuitrin S) as well as to give data comparing activities obtained in the assay of the same preparation by several other recognized methods.

Zondek and Aschheim (1) suggested the use of baby female white mice weighing 6 to 8 Gm., for assaying anterior pituitary sex hormone preparations.

In 1931, Fevold, Hisaw and Leonard (2) published a method for the assay of the anterior pituitary sex hormone using immature female white rats 20 to 25 days old as the test animals. Later, Fevold, *et al.* (3) used 21- to 23-day old rats and the same technique but they also reported that rabbits 12 weeks old were even more

* Scientific Section, A. PH. A., Washington meeting, 1934.

satisfactory, as they were not so susceptible to small amounts of luteinizing hormone as are rats and, consequently, differentiated better between the follicle-stimulating and the luteinizing action.

Wallen-Lawrence and Van Dyke (4) utilized an assay method in which increase in size of the ovaries or seminal vesicles of immature rats is critically determined.

Katzman and Doisy (5) suggest the use of 19-day old female white mice in which a dose given subcutaneously in six equal portions during the course of three days will cause opening of the vagina and *estrus* on the 22nd to the 24th day of age, as judged by vaginal smears, if the dose used contains one or more mouse units. They also used 21-day old rats in which case one rat unit must produce these reactions by the 27th day of age.

Friedman (6) has studied the effect of various agents on ovulation in the rabbit and suggests an assay method for anterior pituitary sex-regulating activity utilizing this physiological response.

Friedman raised the objection to the rat method that rats reach sexual maturity normally at such a variable age that the ovaries of 3-week-old rats will be in such a widely scattered state of development that the same dose of an effective agent could not bring all of them into maturity at the same time. Some attempt has been made recently by Davy (7) to overcome this objection by roughly standardizing the normal uninjected female rats. She found that those animals which weighed between 35 and 45 Gm. at 24 days of age possessed remarkably uniform ovaries, and drew the conclusion that at least one of three such rats may be expected to give a positive response to one M. E. D. of gonadotropic substance injected in 5 daily doses. This will be commented upon further a little later.

Mention might also be made of the contribution by Swezy (8) in which she voices criticism of practically all the assay methods that have thus far been proposed. Nothing of a constructive nature is offered.

EXPERIMENTAL.

In the early work in this laboratory thirty-day old female white rats, taken from a colony the members of which showed an average sexual maturity age of 50 to 60 days, were used for the potency control of experimental extracts containing the sex-regulating activity of the anterior pituitary as found in pregnancy urine. The unknown solution was tested usually at five levels using only two rats at each level. It was soon realized, however, that a method utilizing a relatively small number of animals is of qualitative value only but does not meet the rigid requirements of a commercial assay method. It was also found that more accurate results could be obtained with the use of rats twenty-six days of age. The details of our present method are as follows:

Immature female white rats *26 days* old at the beginning of the test, from a colony with an average normal sexual maturity age of 55 days, are dosed subcutaneously twice a day for thee days and autopsy done 96 to 100 hours after the first dose. At least *5 rats* and *usually 10* are used at each dosage level and a majority (6 out of 10) must show the definite development of one or more corpora lutea for the test to be positive at this level. The weight of the rats and the condition of the vagina and uterus is also carefully noted at the end of the test but the real criterion is the formation of corpora lutea on the ovaries for we have often

found corpora lutea without the vagina being open and sometimes vice versa. Usually four levels of dosage varying 10% to 20% with each other are selected and the smallest dose determined which meets the rigid requirements of the test. A typical protocol is given herewith in detail.

TABLE I.

Antuitrin S, R 849774.

Age.	Dose.	Dil.	Total Volume.	Wt. 30 Da.	Corpora Lutea.	Vagina and Uterus.		Rat U.
26 days	0.83 cc. × 6	1–500	0.01 cc.	40 Gm.	2	Open	Congested	100
...	.....	...	....	42 Gm.	2	Closed	Congested	100
...	.....	...	....	48 Gm.	6	Open		100
...	.....	...	....	44 Gm.	3	Open		100
...	.....	...	....	50 Gm.	7	Open		100
...	0.67 cc. × 6	...	0.008 cc.	48 Gm.	4	Open		125
...	.....	...	....	50 Gm.	4	Open		125
...	.....	...	....	50 Gm.	4	Open		125
...	.....	...	....	50 Gm.	5	Open		125
...	.....	...	....	40 Gm.	2	Closed	Congested	125
...	.....	...	....	40 Gm.	3	Closed	Congested	125
...	.....	...	....	40 Gm.	4	Open	Congested	125
...	.....	...	....	50 Gm.	0	Closed	Congested	125
...	.....	...	....	50 Gm.	4	Open		125
...	.....	...	....	44 Gm.	1	Closed	Congested	125
...	0.55 cc. × 6	...	0.006 cc.	50 Gm.	5	Open		150
...	.....	...	....	48 Gm.	2	Closed	Congested	150
...	.....	...	....	50 Gm.	3	Open	Congested	150
...	.....	...	....	44 Gm.	3	Open	Congested	150
...	.....	...	....	40 Gm.	2	Closed	Congested	150
...	.....	...	....	48 Gm.	6	Open		150
...	.....	...	....	48 Gm.	3	Open	Congested	150
...	.....	...	....	38 Gm.	2	Closed	Congested	150
...	.....	...	....	40 Gm.	3	Open	Congested	150
...	.....	...	....	50 Gm.	0	Closed	Congested	150
...	0.47 cc. × 6	...	0.0057 cc.	48 Gm.	0	Closed	Congested	175
...	.....	...	....	46 Gm.	2	Closed	Congested	175
...	.....	...	....	40 Gm.	1	Closed	Congested	175
...	.....	...	....	40 Gm.	2	Closed	Congested	175
...	.....	...	....	50 Gm.	6	Open	Congested	175
...	.....	...	....	50 Gm.	0	Closed	Congested	175
...	.....	...	....	34 Gm.	0	Closed	Congested	175
...	.....	...	....	46 Gm.	2	Open	Congested	175
...	.....	...	....	50 Gm.	3	Open	Congested	175
...	.....	...	....	50 Gm.	0	Closed	Congested	175
...	0.42 cc. × 6	...	0.0050 cc.	50 Gm.	0	Closed	Congested	200
...	.....	...	....	48 Gm.	0	Closed	Congested	200
...	.....	...	....	50 Gm.	0	Closed	Congested	200
...	.....	...	....	50 Gm.	0	Closed	Congested	200
...	.....	...	....	44 Gm.	0	Closed	Congested	200

Activity is 175 rat units per cc. (6 out of 10 positive).

In addition to the successful quantitative use of the method outlined in the assay of almost 1000 samples both experimental and commercial, we have conducted a rather intensive study of the stability of a particular experimental lot,

R 095286-B, and also of its activity by several methods. By our regular method using immature rats this lot has been tested as follows:

TABLE II.

1.	May 2, 1933	175 rat units per cc.	
2.	May 9, 1933	175	
3.	June 6, 1933	150	5 weeks old
4.	July 6, 1933	150	9 weeks old
5.	Aug. 8, 1933	125	14 weeks old
6.	Aug. 29, 1933	75	17 weeks old
7.	Sept. 19, 1933	75	20 weeks old
8.	Oct. 17, 1933	75	24 weeks old

Careful tests on this lot in September 1933 upon baby mice for results comparable to the Zondek and Doisy mouse units gave data as follow:

TABLE III.

R 095286-B. Female, 15- to 18-day old mice.

Weight. 9/26.	Weight. 9/30.	Dose.	Dil.	Total Volume.	Smear Stage.	Corpora Lutea.	Vagina and Uterus.		Rat Units.
9 Gm.	12 Gm.	0.6 cc. × 6	1–30	0.12 cc.	5	2	Open		8
7 Gm.	11 Gm.	.....	....	....	4	3	Open		
8 Gm.	11 Gm.	.....	....	....	2	2	Open	Congested	
8 Gm.	11 Gm.	.....	....	....	2	1	Open	Congested	
6 Gm.	9 Gm.	.....	....	....	4	1	Open	Congested	
8 Gm.	7 Gm.	.....	....	....	2	0	Open	Congested	
8 Gm.	Died				–				
6 Gm.	Died				–				
10 Gm.	14 Gm.	.....	....	....	5	2	Open		
Male									
6 Gm.	7 Gm.	0.4 cc. × 6	....	0.08 cc.	5	1	Open		12
8 Gm.	10 Gm.	.....	....	....	3	5	Open	Congested	
7 Gm.	11 Gm.	.....	....	....	2	2	Open	Congested	
8 Gm.	12 Gm.	.....	..	....	–	0	Closed		
8 Gm.	10 Gm.	.....	....	....	5	1	Open	Congested	
8 Gm.	7 Gm.	.....	....	....	1–2	4	Open	Congested	
7 Gm.	9 Gm.	.....	....	....	1–2	1	Open	Congested	
6 Gm.	6 Gm.	.....	....	....	1–2	0	Open	Congested	
8 Gm.	10 Gm.	.....	....	....	2	1	Open	Congested	
8 Gm.	Died				...	..			
8 Gm.	10 Gm.	0.33 cc. × 6	....	0.066 cc.	2	1	Open	Congested	15
6 Gm.	Died				...	..			
10 Gm.	11 Gm.	.....	....	....	2	2	Open	Congested	
8 Gm.	10 Gm.	.....	....	....	1–2	2	Open	Congested	
7 Gm.	9 Gm.	.....	....	....	2	2	Open	Congested	
7 Gm.	9 Gm.	.....	....	....	2	0	Open	Congested	
9 Gm.	13 Gm.	.....	....	....	1–2	4	Open	Congested	
6 Gm.	9 Gm.	.....	....	....	4	0	Open		
7 Gm.	10 Gm.	.....	....	....	1–2	1	Open	Congested	
7 Gm.	Died				...	..			
8 Gm.	11 Gm.	0.25 cc. × 6	....	0.05 cc.	1–2	2	Open	Congested	20
8 Gm.	12 Gm.	.....	....	....	...	0	Closed	Congested	
8 Gm.	12 Gm.	.....	....	....	...	0	Closed	Congested	
7 Gm.	8 Gm.	.....	....	....	1–2	2	Open	Congested	
9 Gm.	12 Gm.	.....	....	....	2	2	Open	Congested	
7 Gm.	10 Gm.	.....	....	....	...	0	Closed	Congested	

TABLE III.—*Continued.*

Weight. 9/26.	9/30.	Dose.	Dil.	Total Volume.	Smear Stage.	Corpora Lutea.	Vagina and Uterus.		Rat Units.
8 Gm	12 Gm.	.....	....	....	...	1	Closed	Congested	
8 Gm	10 Gm.	.....	....	....	...	0	Closed	Congested	
7 Gm	Died					..			
8 Gm	12 Gm.	.....	....	....	2	2	Open	Congested	
10 Gm.	12 Gm.	0.16 cc. × 6	....	0.032 cc.	4?	0	Open	Congested	30
6 Gm.	8 Gm.	.....	....	....	...	0	Closed	Congested	
8 Gm.	12 Gm.	.....	....	....	1–2	2	Open	Congested	
8 Gm.	14 Gm.	.....	....	....	...	0	Closed	Congested	
7 Gm.	12 Gm.	.....	....	....	...	0	Closed		
8 Gm.	12 Gm.	.....	....	....	1–2	2	Open	Congested	
6 Gm.	10 Gm.	.....	....	....	...	0	Closed	Congested	
8 Gm.	12 Gm.	.....	....	....	...	0	Closed	Congested	
6 Gm.	9 Gm.	.....	..	....	...	0	Closed	Congested	
8 Gm.	14 Gm.	.. ..	....	....	2	1	Open	Congested	

Five out of 9 were positive at 20 units per cc. and only 3 out of 10 were positive at 30 units, so 20 mouse units per cc. is the activity of Ꝑ 095286-B. Since this lot assayed 75 and 80 rat units per cc. after August 8, 1933, 1 mouse unit is approximately equal to 4 rat units.

A very recent check test on baby mice at the two critical levels of comparison resulted as follows:

TABLE IV.

Ꝑ 095286-B. Assaying 80 R. U./cc.

Female white mice approx. 16 days old.

Weight. 10/27.	10/21.	Dose.	Dil.	Total Volume.	Corpora Lutea.	Vagina and Uterus.		Mouse Units.	Ratio R. U.:M. U.
8 Gm.	10 Gm.	0.33 cc. × 6	1–30	0.066 cc.	1	Closed	Congested	15	1:5
8 Gm.	11 Gm.	.....	....	...	0	Closed	No effect	15	1:5
7 Gm.	8 Gm.	.....	....	...	2	Closed	Congested	15	1:5
7 Gm.	8 Gm.	.....	....	...	0	Closed	Congested	15	1:5
9 Gm.	10 Gm.	....	....	...	2	Closed	Congested	15	1:5
9 Gm.	11 Gm.	.....	....	...	2	Closed	Congested	15	1:5
7 Gm.	9 Gm.	.....	....	...	2	Closed	Congested	15	1:5
8 Gm.	11 Gm.	.....	....	...	1	Closed	Congested	15	1:5
8 Gm.	8 Gm.	.....	....	...	1	Closed	Congested	15	1:5
7 Gm.	8 Gm.	.....	....	...	0	Closed	No effect	15	1:5
7 Gm.	9 Gm.	0.25 cc. × 6	....	0.050 cc.	0	Closed	No effect	20	1:4
7 Gm.	8 Gm.	.....	....	...	0	Closed	No effect	20	1:4
8 Gm.	10 Gm.	.....	....	...	0	Closed	No effect	20	1:4
8 Gm.	10 Gm.	.....	....	...	2	Open	Congested	20	1:4
9 Gm.	11 Gm.	.....	....	...	1	Closed	Congested	20	1:4
10 Gm.	12 Gm.	.....	....	...	2	Closed	Congested	20	1:4
8 Gm.	10 Gm.	.....	....	...	1	Closed	Congested	20	1:4
8 Gm.	9 Gm.	.....	....	...	0	Closed	No effect	20	1:4

70% were positive at 15 rat units per cc. or 1 mouse unit = 5 rat units.
50% were positive at 20 rat units per cc. or 1 mouse unit = 4 rat units.

Only one mouse was positive out of 18 by the Katzman-Doisy technique and that was with the smaller dose of the two.

Some preliminary work on mice a year previously showed that at 5 and 6 rat units per mouse unit only 50% of the mice were positive but this later relationship is more convincing and probably more nearly correct.

This lot was also tested on 21-day old white rats with observation of vaginal smears at the end of the fourth day after the first injection in order to conform closely to the Katzman-Doisy technique for the purpose of comparing our unit with their rat unit. Results of this test are given in Table V.

TABLE V.

B 095286-B. (21-day old rats, Katzman-Doisy technique.)

Weight. Before.	Weight. After.	Dose.	Dil.	Total Volume.	Smear Stage.	Corpora Lutea.	Vagina and Uterus.		Rat Units.
35 Gm.	47 Gm.	0.8 cc. × 6	1–100	0.048 cc.	2	2	Open	Congested	20
32 Gm.	40 Gm.	....	.....	...	3	2	Open	Congested	..
25 Gm.	35 Gm.	....	.....	...	3	3	Open	Congested	..
30 Gm.	38 Gm.	....	.....	...	2	1	Open	Congested	..
20 Gm.	Died				...	..			
35 Gm.	38 Gm.	0.4 cc. × 6	.....	0.024 cc.	2	2	Open		40
36 Gm.	42 Gm.	....	.....	...	2	3	Open		..
28 Gm.	30 Gm.	....	.....	...	...	0	Closed	Congested	..
30 Gm.	35 Gm.	....	.....	...	3	0	Open	Congested	..
30 Gm.	40 Gm.	....	.....	...	...	3	Closed	Congested	..
28 Gm.	30 Gm.	....	.....	...	2	3	Open	Congested	..
30 Gm.	40 Gm.	....	.....	...	2	2	Open	Congested	..
30 Gm.	38 Gm.	....	.....	...	3	2	Open	Congested	..
28 Gm.	38 Gm.	....	.....	...	3	3	Open	Congested	..
25 Gm.	38 Gm.	....	.....	...	2	2	Open	Congested	..
25 Gm.	36 Gm.	0.8 cc. × 6	1–300	0.016 cc.	2	2	Open	Congested	60
36 Gm.	44 Gm.	....	.....	...	1–2		Open	Congested	..
30 Gm.	40 Gm.	....	.....	...	2	1	Open	Congested	..
35 Gm.	43 Gm.	....	.....	...	...	0	Closed	Congested	..
25 Gm.	30 Gm.	....	.....	...	...	0	Closed	Congested	..
30 Gm.	40 Gm.	....	.....	...	1–2	2	Open	Congested	..
36 Gm.	42 Gm.	....	.....	...	...	0	Closed	Congested	..
30 Gm.	38 Gm.	....	.....	...	1–2	2	Open	Congested	..
25 Gm.	33 Gm.	....	.....	...	1–2	1	Open	Congested	..
30 Gm.	35 Gm.	....	.....	...	...	0	Closed	Congested	..
40 Gm.	48 Gm.	0.6 cc. × 6	.....	0.012 cc.	...	0	Closed	Congested	..
45 Gm.	50 Gm.	....	.....	...	...	3	Closed	Congested	..
30 Gm.	36 Gm.	....	.....	...	...	0	Closed	Congested	..
40 Gm.	50 Gm.	....	.....	...	...	0	Closed	Congested	83
34 Gm.	36 Gm.	....	.....	...	...	4	Closed	Congested	..
30 Gm.	38 Gm.	....	.....	...	...	4	Closed	Congested	..
25 Gm.	35 Gm.	....	.....	...	...	3	Closed	Congested	..
25 Gm.	33 Gm.	....	.....	...	...	1	Closed	Congested	..
20 Gm.	30 Gm.	....	.....	...	...	0	Closed	Congested	..
25 Gm.	33 Gm.	....	.....	...	...	0	Closed	Congested	..
47 Gm.	55 Gm.	0.5 cc. × 6	.....	0.010 cc.	...	0	Closed	Congested	100
35 Gm.	43 Gm.	....	.....	...	...	1	Closed	Congested	..
35 Gm.	40 Gm.	....	.....	...	...	0	Closed	Congested	..
25 Gm.	33 Gm.	....	.....	...	...	0	Closed	Congested	..
30 Gm.	40 Gm.	....	.....	...	...	2	Closed	Congested	..

Activity is 60 Doisy rat units per cc.

Activity is 60 to 80 Parke, Davis rat units per cc. on the 21-day old rats or 75 P. D. rat units per cc. on 26- to 28-day old rats.

The Doisy and Parke, Davis rat units are apparently very nearly equal even though the details of the two methods vary materially. To prove further that

these two units are about the same and that assays of the same preparation conducted in different laboratories can agree very closely, the following series of tests made in Dr. Doisy's and in our laboratories is given in Table VI.

TABLE VI.

Antuitrin S.

Sample No.	Our Assay. Date.	Our Assay. Rat Units.	Dr. Doisy's Assay. Date.	Dr. Doisy's Assay. Rat Units.
3008439	5/22/33	175	6/14/33	165
3008440	6/10/33	175	6/26/33	167
3009703	6/10/33	175	7/8/33	166
3009702	6/17/33	175	7/8/33	166
3010507	7/1/33	100	7/29/33	75
3013846	7/22/33	150	8/5/33	166
3013847	7/29/33	150	8/10/33	133
3015303	8/5/33	175	8/18/33	166
3016294	8/12/33	100	9/2/33	133
3014538	8/12/33	150	9/2/33	166
3016295	9/19/33	100	9/12/33	85
3016852	8/26/33	175	9/12/33	166
3017466	9/2/33	125	9/18/33	133
3018030	9/2/33	175	9/18/33	166

The agreement in the above assay values obtained in two different laboratories by methods that are not identical is indeed remarkable. The slight variations are largely due to differences in selection of dosage levels.

THE FRIEDMAN RABBIT OVULATION METHOD.

One of us (W. O. N.) has carefully studied the activity of this particular lot of Antuitrin S, Ⱥ 095286-B, by the Friedman method with results that may be tabulated as follows:

TABLE VII.

Ⱥ 095286-B. Rabbit Ovulation Tests.
Estrous Animals Including Postpartum Cases.

Weight Kg.	Actual Dose per Kg.	Result.
3.2 pp	0.56 R. U.	−
3.0	0.60 R. U.	−
3.0	0.60 R. U.	−
4.1 pp	0.60 R. U.	−
3.2 pp	0.60 R. U.	−
3.95	0.75 R. U.	−
4.2	0.75 R. U.	−
4.2 pp	0.75 R. U.	−
3.6 pp	0.84 R. U.	−
3.65	0.90 R. U.	+
2.5	0.90 R. U.	−
2.5	0.90 R. U.	−
2.4	0.90 R. U.	−
4.1	0.90 R. U.	−
4.1 pp	0.90 R. U.	+
3.5 pp	0.90 R. U.	+
3.25 pp	0.90 R. U.	−
3.85 pp	0.90 R. U.	+
3.27 pp	0.96 R. U.	+
3.8	0.96 R. U.	−
3.7	0.96 R. U.	+
3.5	0.96 R. U.	+
3.25 pp	0.96 R. U.	+
3.3 pp	0.96 R. U.	+
4.2 pp	0.96 R. U.	+
3.1	1.002 R. U.	+
3.5	1.02 R. U.	+
4.1	1.02 R. U.	+
3.8	1.05 R. U.	+
2.5	1.05 R. U.	+
2.65 pp	1.05 R. U.	+
3.0	1.05 R. U.	+
3.5 pp	1.05 R. U.	+
3.0	1.20 R. U.	+
2.7	1.20 R. U.	+
3.1	1.20 R. U.	+
2.75	1.20 R. U.	+
3.2	1.20 R. U.	+
2.5	1.20 R. U.	+
2.85	1.50 R. U.	+
2.4	1.80 R. U.	+
3.1	2,46 R. U.	+
2.70	3.70 R. U.	+

pp = postpartum animals.
+ = ovulation.
− = no ovulation.

Actual dose means dose figured on the basis of the assay of 75. R. U. per cc. Assay conducted without knowledge of actual potency.

Table VII indicates a slightly greater sensitivity on the part of postpartum animals since at the 0.90 R. U. per Kg. level 3 out of 4 postpartum animals ovulated while only 1 out of 5 of the ordinary isolated females did so, and at 0.96 R. U. per Kg. all 4 of the postpartum animals ovulated while only 2 out of 3 of the others did so. Also a few of the animals were used 2 or more times if they did not ovulate with the first dose, but Friedman has demonstrated that such animals are not rendered more susceptible to subsequent doses.

TABLE VIII.

Non-estrous Rabbits.

Weight Kg.	Actual Dose per Kg.	Result.
3.1	1.2 R. U.	–
2.4	1.2 R. U.	–
2.9	1.2 R. U.	–
2.75	1.2 R. U.	–
4.1	1.2 R. U.	–
2.5	1.8 R. U.	–
3.0	3.0 R. U.	–
2.2	3.0 R. U.	–
2.27	3.0 R. U.	–
2.8	3.0 R. U.	–
2.8	4.5 R. U.	–
2.5	4.5 R. U.	+
2.3	6.0 R. U.	+
3.2	6.0 R. U.	+
2.85	6.0 R. U.	–
2.8	6.0 R. U.	+
2.4	9.0 R. U.	+
2.8	12.0 R. U.	+
2.95	12.0 R. U.	+

These animals were classified as non-estrous because their ovaries contained recent corpora lutea. These corpora lutea had been formed by previous Antuitrin-S injections or the injection of some one of the Antuitrin-L extracts. However, there was every reason to believe that ovulation might be induced, if the dose of Antuitrin-S were large enough, since fairly large follicles were present in the ovaries along with the corpora lutea.

TABLE IX.

Young Animals.

Weight Kg.	Actual Dose per Kg.	Result.
1.85	6.0 R. U.	–
1.80	6.0 R. U.	–
1.9	9.0 R. U.	–
1.85	9.0 R. U.	–
2.05	12.0 R. U.	+
1.90	12.0 R. U.	+
2.1	12.0 R. U.	+

This table gives data on a very limited number of young animals approaching maturity which indicate that about 12 R. U. per Kg. are necessary to induce ovulation.

SUMMARY OF RABBIT OVULATION RESULTS.

TABLE X.

Estrous and Postpartum Animals.

Actual Dose Injected per Kg.	Number of Cases. Positive.	Negative.
0.56 R. U.	0	1
0.60 R. U.	0	4
0.75 R. U.	0	3
0.84 R. U.	0	1
0.90 R. U.	4	5
0.96 R. U.	6	1
1.002 R. U.	1	0
1.02 R. U.	2	0
1.05 R. U.	5	0
1.20 R. U.	6	0
1.50 R. U.	1	0
1.80 R. U.	1	0
2.46 R. U.	1	0
3.70 R. U.	1	0

TABLE XI.

Non-estrous Animals.

Actual Dose Injected per Kg.	Number of Cases. Positive.	Negative.
1.2 R. U.	0	5
1.8 R. U.	0	1
3.0 R. U.	0	4
4.5 R. U.	1	1
6.0 R. U.	3	1
9.0 R. U.	1	0
12.0 R. U.	2	0

TABLE XII.—Young Animals.

Actual Dose Injected per Kg.	Number of Cases. Positive.	Negative.
6.0 R. U.	0	2
9.0 R. U.	0	2
12.0 R. U.	3	0

In each injection for the induction of ovulation the desired quantity of the extract was taken and made up to 1 cc. Injections were given intravenously and the response was determined in 24 to 36 hours by operation or autopsy.

DISCUSSION.

The tabulated experimental data submitted serve to show the practicability of the proposed method using immature white rats (26 to 28 days old for the control of the sex-regulating activity of the anterior pituitary with an accuracy of 10% to 20%. In our opinion the use of rats of this age with autopsy at 96 to 100 hours after the first dose and examination for mature corpora lutea is more definite and practical than the use of younger rats with dependence on the opening of the vagina and upon the estrous stage for a positive reaction, or the use of baby mice where determination of mature corpora lutea is much more difficult.

We do find from assays of the same preparations in different laboratories by our corpora lutea method on 26- to 28-day old rats and by the estrous stage method on 21-day old rats (Doisy) that very good agreement in values can be obtained by the two methods.

As for the methods using baby white mice, we do not find them any more accurate and certainly they are less practical both because of greater difficulty in interpreting results by gross observation, and also because proper test animals cannot be secured very readily.

The rabbit ovulation method appears to be of value and we have provided a basis of comparison between results obtained by it and by the other methods. It is to be noted that our results check closely those reported by Dr. Friedman. However, it does not seem to possess any advantages over the other methods as to accuracy or specificity of the positive reaction and it is more time-consuming and expensive particularly if twenty rabbits are to be used in a test. Friedman's objection to the rat methods that different rats reach sexual maturity at such a variable age is taken care of by the use of a number of rats (5 to 10) at each dosage level and by requiring that only a bare majority be positive at the end of the test, for it is admitted that some individual animals are backward in their ovarian development and could not be brought into sexual maturity by the minimum effective dose for the majority.

SUMMARY.

1. A practical and accurate method is presented for the standardization of the anterior pituitary-like sex hormone from pregnancy urine.

2. The relationship between our rat unit and the mouse unit has been shown experimentally to be about 1 mouse unit equivalent to 4 rat units.

3. The rabbit ovulation unit was found experimentally to be equivalent to 1 rat unit per Kg. body weight of rabbit.

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FROM THE RESEARCH LABORATORIES,
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DRUG EXTRACTION. I. A STUDY OF VARIOUS MENSTRUA FROM THE STANDPOINT OF SWELLING EFFECTS, PENETRATION AND EXTRACTION.[1, 2, 3]

BY WILLIAM J. HUSA[4] AND LOUIS MAGID.

INTRODUCTION.

The extraction of drugs is a time-honored process. However, there has been a feeling in recent years that the fundamental principles involved in this basic pharmaceutical procedure have received insufficient attention. Such factors as the swellings of drugs in liquids and the penetration of menstrua have not been studied quantitatively and many official formulas are based to a considerable extent on empiricism and tradition.

The purpose of the present investigation has been to make a critical study of the fundamental principles of drug extraction with special reference to permeation of cell walls by a selected series of pharmaceutical solvents, to swelling of cellular tissue during maceration with selected menstrua, and to the influence of menstrua upon the structure of vegetable drugs and extraction of the constituents.

SWELLING EFFECT OF SOLVENTS.

Chestnut wood, being a relatively simple vegetable structure, was chosen as the first material to be studied with the idea that the methods evolved and the data collected would be applied in the course of the investigation in the study of various types of drugs. Chestnut wood consists largely of fibrous tissue and one of its constituents is tannin.

Swelling of Strips of Chestnut Wood.—A study of the swelling effect of solvents on thin sections was deemed advisable as the first point of attack. The liquids

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[1] Scientific Section, A. PH. A., Washington meeting, 1934.

[2] This investigation was aided by a grant from the AMERICAN PHARMACEUTICAL ASSOCIATION Research Fund.

[3] This paper is based on a dissertation submitted by Louis Magid to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[4] Head Professor of Pharmacy, University of Florida.

customarily used to soften hard tissues for sectioning, such as solutions of hydrofluoric acid, potassium hydroxide, etc., obviously could not be used. By the use of a "smoother" at a planing mill, thin cross-section shavings, suitable for microscopical study, were obtained. A plan was devised of cutting a strip of a section of chestnut wood, 0.25 to 0.50 mm. wide, so that the strip could be observed in the field of the microscope under low power and measurements made with a filar micrometer of the width of the strip before and after the addition of solvents. The width of the strips ranged from 0.14 to 0.65 mm., and the length from 3 to 6 mm. The thickness of the strips ranged from 0.045 to 0.070 mm. The strips examined consisted largely of summer wood, inasmuch as strips of spring wood generally tore on the addition of water. Measurements of swelling were made in units of the filar micrometer and for concise presentation in the tables which follow all results have been recalculated on a percentage basis with the width of the dry strip taken as 100. The results given are the average of 3 or more determinations in each case.

Effect of Various Menstrua on Strips of Chestnut Wood.—Scoville (1) has listed 20 different alcohol-water mixtures used as menstrua in official preparations and has suggested that some of these which differ slightly in percentage strength could well be eliminated. From this list, 8 alcohol-water mixtures were selected and their effect on the width of strips of chestnut wood was determined. Glycerin-water and glycerin-alcohol mixtures were studied similarly.

The results in Table I indicate that mixtures of equal volumes of alcohol and water and mixtures containing less than this proportion of alcohol have practically the same swelling effect as water alone, causing an immediate swelling with very little further change during the two hours. The weaker alcoholic menstrua apparently reach a swelling equilibrium within a few minutes. With concentrations of alcohol exceeding 58 per cent by volume there is an increasing tendency toward a smaller immediate swelling and a more gradual approach to equilibrium (see Graph 1).

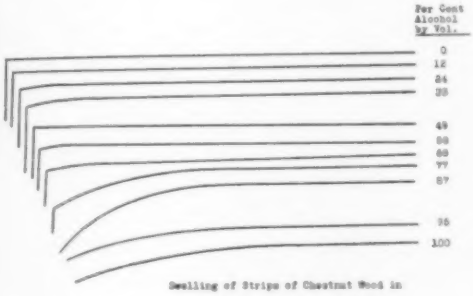
TABLE I.—EFFECT OF VARIOUS ALCOHOL-WATER MIXTURES.

Per Cent, Alcohol by Volume.	Dry.	After Time Intervals (Minutes).								
	0.	1.	5.	10.	20.	40.	60.	80.	100.	120.
0 (Water)	100	120	120	120	120	120	120	120	120	120
11.8	100	118	119	119	119	121	120	118	118	118
24.0	100	119	119	120	120	121	121	120	120	120
32.8	100	121	122	122	123	124	124	124	124	124
49.0	100	117	116	116	116	116	116	116	116	116
58.4	100	114	115	115	115	115	115	115	115	116
68.1	100	112	112	113	113	114	114	114	115	115
77.4	100	108	111	113	115	118	120	120	120	120
86.5	100	101	105	110	115	118	121	121	121	121
95.2	100	101	102	102	107	107	109	110	110	110
99.9	100	99	100	102	104	108	109	110	110	110

The results in Table II indicate that a mixture of 1 volume of glycerin and 7 volumes of water has practically the same effect as water alone. With increasing concentrations of glycerin the primary rise decreases and a longer time is required for equilibrium to be reached. Glycerin alone and a mixture of glycerin 9 volumes and water 1 volume both cause an immediate swelling of about 1 per cent with no further change during two hours (see Graph 2).

TABLE II.—EFFECT OF VARIOUS GLYCERIN-WATER MIXTURES.

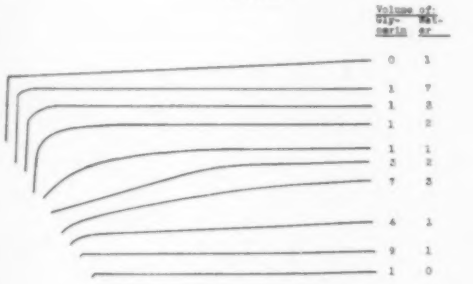
Volume of Glycerin.	Volume of Water.	Dry. 0.	After Time Intervals (Minutes). 1.	5.	10.	20.	40.	60.	80.	100.	120.
0	1	100	120	120	120	120	120	120	120	120	120
1	7	100	122	124	124	124	124	124	124	124	124
1	3	100	116	119	121	121	121	121	121	121	121
1	2	100	113	119	120	121	122	122	122	122	122
1	1	100	103	106	108	112	114	116	116	116	116
3	2	100	101	102	103	106	111	115	116	117	117
7	3	100	103	103	105	108	111	114	116	117	118
4	1	100	103	103	103	104	105	106	107	108	109
9	1	100	101	101	101	101	101	101	101	101	101
1	0	100	101	101	101	101	101	101	101	101	101



Swelling of Strips of Chestnut Wood in Various Alcohol-Water Mixtures.

For numerical data see table 1.

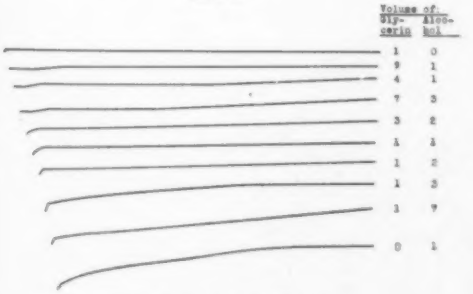
Graph 1.



Swelling of Strips of Chestnut Wood in Various Glycerin-Water Mixtures.

For numerical data see table 2.

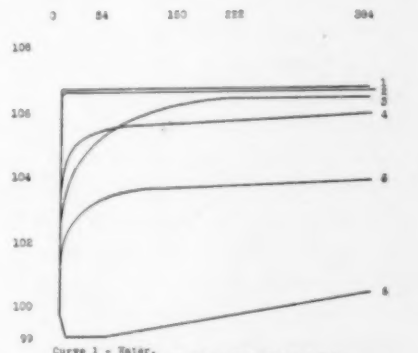
Graph 2.



Swelling of Strips of Chestnut Wood in Various Glycerin-Alcohol Mixtures.

For numerical data see table 3.

Graph 3.

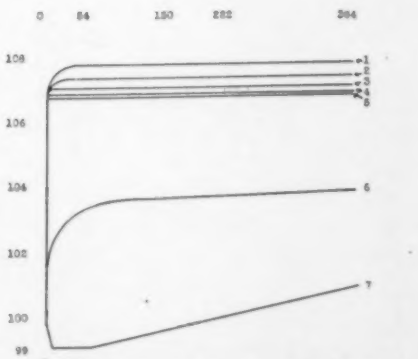


Curve 1 - Water.
Curve 2 - Mixture Alcohol 1 Vol.-Water 1 Vol.
Curve 3 - Mixture Glycerin 1 Vol.-Alcohol 1 Vol.
Curve 4 - Mixture Glycerin 1 Vol.-Water 1 Vol.
Curve 5 - Alcohol.
Curve 6 - Glycerin.

Swelling of Chestnut Wood Blocks in Solvents.
Swelling Expressed on Basis of Original Thickness = 100.

Abscissa: Time in Hours.
Ordinates: Percentage Swelling or Shrinking Based on Dry = 100.

Graph 4.



Curves:
1 - Mixt. Glycerin 75 Vol.-Alcohol 675 Vol.-Water 250 Vol.
2 - Mixt. Glycerin 1 Vol.-Alcohol 5 Vol.-Water 4 Vol.
3 - Mixt. Glycerin 1 Vol.-Alcohol 3 Vol.-Water 5 Vol.
4 - Mixt. Glycerin 66 Vol.-Alcohol 250 Vol.-Water 668 Vol.
5 - Water.
6 - Alcohol.
7 - Glycerin.

Swelling of Chestnut Wood Blocks in Solvents.
Swelling Expressed on Basis of Original Thickness = 100.

Abscissa: Time in Hours.
Ordinates: Percentage Swelling or Shrinking Based on Dry = 100.

Graph 5.

TABLE III.—EFFECT OF VARIOUS GLYCERIN-ALCOHOL MIXTURES.

Volume of Glycerin.	Volume of Alcohol.	Dry.	After Time Intervals (Minutes).								
		0.	1.	5.	10.	20.	40.	60.	80.	100.	120.
1	0	100	101	101	101	101	101	101	101	101	101
9	1	100	100	100	100	101	101	101	101	101	101
4	1	100	100	100	101	101	101	101	102	103	103
7	3	100	100	100	101	101	101	102	103	104	105
3	2	100	101	102	102	102	103	103	103	104	104
1	1	100	102	103	103	103	104	104	104	105	105
1	2	100	102	102	102	103	104	105	105	106	106
1	3	100	103	104	105	105	108	109	110	110	111
1	7	100	102	103	104	104	106	108	110	112	114
0	1	100	101	102	102	107	107	109	110	110	110

The results in Table III indicate that there is practically no swelling with glycerin and with a mixture of 9 volumes of glycerin and 1 volume of alcohol. With increasing concentrations of alcohol there is an increase in the rate and amount of swelling (see Graph 3).

Effect of Acidity and Alkalinity on Swelling of Strips of Chestnut Wood.—There is abundant evidence in the literature showing that acidity and alkalinity are important factors in the swelling of colloids and plant tissues. In view of these facts and the established use of acids in menstrua of some official extractive preparations, it seemed desirable to know whether changes in acidity and alkalinity affect the swelling of drugs. Using sodium hydroxide and hydrochloric acid, distilled water was adjusted to a series of p_H values by the colorimetric method with LaMotte indicators and standards. The effect of these liquids on the swelling of strips of chestnut wood is shown in Table IV.

TABLE IV.—EFFECT OF WATER ADJUSTED TO VARIOUS p_H VALUES.

p_H of Water.	Dry.	After Time Interval (Minutes).								
	0.	1.	5.	10.	20.	40.	60.	80.	100.	120.
0.9	100	121	121	121	121	121	121	121	121	121
1.9	100	120	120	120	120	120	120	120	120	120
3.1	100	121	121	122	122	122	122	122	122	122
4.7	100	120	120	120	120	120	120	120	120	120
5.7	100	120	120	120	120	120	120	120	120	120
6.9	100	120	120	120	120	120	120	120	120	120
7.5	100	120	121	121	121	121	121	121	121	121
8.9	100	122	122	123	123	123	123	123	123	123
10.5	100	120	121	121	121	121	121	122	122	122
12.0	100	119	121	122	122	123	123	123	123	123

From the above results it is seen that a variation in p_H of aqueous solutions from 0.9 to 12.0 has practically no effect on the swelling of simple woody tissue such as chestnut wood.

TABLE V.—EFFECT OF ACIDITY AND ALKALINITY OF ALCOHOL.

Alcoholic Solution.	Dry.	After Time Intervals (Minutes).								
	0.	1.	5.	10.	20.	40.	60.	80.	100.	120.
Alcohol alone	100	101	102	102	107	107	109	110	110	110
0.01*N* NaOH	100	100	101	102	107	111	112	113	113	113
0.1*N* NaOH	100	102	103	105	108	113	115	117	117	117
0.01*N* HCl	100	100	101	102	105	107	108	108	108	108
0.1*N* HCl	100	101	102	102	102	102	103	104	104	105

The effect of varying the acidity and alkalinity of alcohol on the swelling of strips of chestnut wood is shown in Table V.

The results indicate that in alcoholic solutions, an increase in alkalinity increases the swelling of strips of chestnut wood, while an increase in acidity decreases the swelling normally caused by alcohol.

Effect of Successive Addition of Liquids on Strips of Chestnut Wood.—The technique employed for determining the effect of successive addition of various liquids on the swelling of chestnut wood strips was that of adding the first liquid during a definite period of time to the strip, removing as much as possible of the liquid by means of filter paper, and then adding the second liquid, etc. The effect of successive additions of water, alcohol and absolute alcohol on strips of chestnut wood are shown in the following tables.

TABLE VI.—EFFECT OF SUCCESSIVE ADDITION OF WATER, ALCOHOL AND ABSOLUTE ALCOHOL.

Time in Minutes.	Dry.	Water.				Alcohol.					Abs. Alc.	
	0.	1.	5.	1.	5.	10.	20.	40.	60.		1.	5.
Average of 2 strips	100	114	115	112	112	112	112	113	114		110	111

It is seen that alcohol shrinks a strip swollen by water, and then causes a gradual swelling. The addition of absolute alcohol at this point causes a shrinking.

TABLE VII.—EFFECT OF SUCCESSIVE ADDITION OF ALCOHOL AND WATER.

Time in Minutes.	Dry.	Alcohol.						Water.	
	0.	1.	5.	10.	20.	40.	60.	1.	5.
Average of 2 strips	100	101	102	103	105	109	114	124	127

The results show that alcohol causes the characteristic gradual swelling; the addition of water after one hour causes an immediate marked increase in swelling.

Experiments were also carried out on the successive addition of liquids as follows: (*a*) absolute alcohol, alcohol and water, (*b*) alcohol and absolute alcohol, (*c*) water and absolute alcohol and (*d*) absolute alcohol and water. Each liquid tended to exert its own effect regardless of whether this resulted in an increase or decrease of the swelling caused by the previously added liquid.

Swelling Effect of Various Liquids on Extracted Strips of Chestnut Wood.—To obtain materials for these tests, cross sections of chestnut wood were exhaustively extracted with water and with alcohol, until the presence of tannin in the extraction liquids was no longer detected. The sections were then air-dried and used in the following experiments, using the technique of measuring the width of strips with a filar micrometer. The following tables show the effect of various liquids and the successive addition of various liquids on strips of extracted chestnut wood. The results in each case are the average of 3 or more determinations.

TABLE VIII.—EFFECT OF VARIOUS LIQUIDS ON EXTRACTED STRIPS OF CHESTNUT WOOD.

Liquid.	Dry.	After Time Intervals (Minutes.)									
	0.	1.	5.	10.	20.	40.	60.	80.	100.	120.
Water	100	118	119	119	119	119	119	119	119	119
5 per cent aqueous solution of tannin	100	119	120	120	120	120	120	120	120	120
Glycerin	100	100	100	100	100	100	100	101	101	101

TABLE IX.—EFFECT OF SUCCESSIVE ADDITION OF VARIOUS LIQUIDS ON EXTRACTED STRIPS OF CHESTNUT WOOD.

Abbreviations: alc. = alcoholic; sol. = solution; N = normal.

	Time in Minutes.																
0.	1.	5.	10.	20.	40.	60.	120.	1.	5.	10.	20.	40.	1.	5.	10.	20.	40.
Dry.	Alcohol.							0.1N alc. HCl					Alcohol.				
100	101	103	104	106	108	110	110	110	110	110	110	110	110	110	110	110	110
Dry.	Alcohol.							0.1N alc. NaOH.					Alcohol.				
100	101	102	103	104	107	109	109	109	109	110	110	111	111	111	110	110	110
Dry.	0.1N alc. HCl.							Alcohol.									
100	101	102	103	105	107	107	107	108	108	108	108	108					
Dry.	5 per cent alc. sol. tannin.							Alcohol.									
100	101	102	103	103	105	106	107	107	107	107	108	108					

Since the extracted strips of chestnut wood showed the same degree of swelling with various liquids as the unextracted strips, it is apparent that treatment with water and alcohol causes no permanent change in the structure of the tissues, or at least no change capable of affecting the swelling properties; it is also apparent that the soluble constituents of this tissue are of no importance in swelling, although a 5 per cent solution of tannin in alcohol decreased the swelling to a slight extent. The results in Table IX show that on successive addition of liquids, usually each liquid tends to exert its own effect regardless of whether this results in an increase or decrease of the swelling caused by the previously added liquid.

Swelling of Blocks of Chestnut Wood.—The swelling of blocks of chestnut wood immersed in various solvents was studied. The wood was cut into uniform 24-mm. blocks, with the grain running the long way, and varying from 1.75 to 1.80 mm. in thickness at the center (across the grain). Three blocks were placed in each solvent in stoppered flasks kept at a constant temperature of 30° C. in a Freas large size water thermostat. The blocks were weighted below the surface of the liquids by pieces of glass rod fastened by a thread. The amount of swelling was based on the change in thickness (across grain), measurements being made with a micrometer caliper. The results obtained from the effects of various liquids on the swelling of blocks of chestnut wood are given in Table X. The results have been recalculated on a percentage basis, with the original thickness of the dry blocks taken as 100, and are based on the average of 3 blocks.

TABLE X.—EFFECT OF VARIOUS LIQUIDS ON BLOCKS OF CHESTNUT WOOD.

Abbreviations: alc. = alcohol; abs. = absolute; gly. = glycerin; mixt. = mixture; v. = volume.

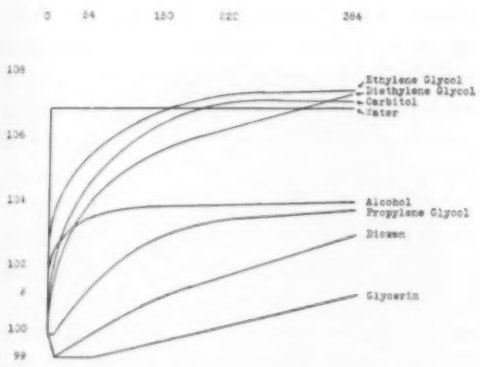
Liquid.	Dry.	After Time Intervals (Hours).						
	0.	6	12.	24.	54.	150.	222.	384.
Water	100	106.9	106.9	106.9	106.9	106.9	106.9	106.9
Alcohol	100	102.6	102.8	102.9	103.6	103.7	103.9	104.0
Glycerin	100	99.3	99.3	99.3	99.3	100.0	100.3	101.1
Dioxan	100	99.3	99.4	99.5	99.8	101.3	101.8	103.0
Carbitol	100	101.3	102.7	103.5	104.4	106.5	107.1	107.1
Diethylene glycol	100	101.0	101.8	102.8	104.0	105.6	106.3	107.3
Propylene glycol	100	100.0	100.2	100.4	101.7	102.8	103.5	103.7
Ethylene glycol	100	103.7	104.0	104.5	105.3	107.0	107.3	107.4
0.01*N* aqueous HCl	100	107.5	107.6	107.6	107.5	107.7	107.7	107.8
0.01*N* aqueous NaOH	100	107.8	107.8	107.8	107.8	107.9	107.9	107.9
0.01*N* alcoholic HCl	100	102.2	102.5	103.0	103.5	103.9	103.9	103.9
0.01*N* alcoholic NaOH	100	102.2	102.7	102.9	103.2	103.3	103.3	103.3
Mixt. alc. 1 v.—water 1 v.	100	106.7	106.8	106.8	106.8	106.8	106.8	106.8
Mixt. gly. 1 v.—water 1 v.	100	104.6	105.2	105.6	105.7	105.8	106.1	106.1
Mixt. gly. 1 v.—alc. 1 v.	100	103.4	104.1	105.3	105.4	106.0	106.6	106.6
Mixt. gly. 1 v.—alc. 5 v.—water 4 v.	100	107.2	107.4	107.4	107.5	107.5	107.5	107.5
Mixt. gly. 1 v.—alc. 3 v.—water 5 v.	100	107.1	107.2	107.2	107.2	107.2	107.2	107.2
Mixt. gly. 75 v.—alc. 675 v.—water 250 v.	100	107.3	107.4	107.9	107.9	107.9	107.9	107.9
Mixt. gly. 65 v.—alc. 250 v.—water 685 v.	100	107.0	107.0	107.0	107.0	107.0	107.0	107.0

The results of the above table show that water causes greater swelling than alcohol, and alcohol causes greater swelling than glycerin. Considering the binary mixtures of water, alcohol and glycerin, we find that a mixture of alcohol 1 vol.—

water 1 vol. produces a swelling equal to that of water, but not reaching equilibrium quite as rapidily. A mixture of equal parts of glycerin and alcohol produces greater swelling than a mixture of equal parts of glycerin and water, but the rate of swelling is slower (see Graph 4).

The ternary mixtures of water, alcohol and glycerin cause a slightly greater swelling than that brought about by water. The ternary mixtures used are 4 of the glycerin-alcohol-water mixtures used in U. S. P. and N. F. extractions. The results indicate that the variations in the 4 official menstrua studied have practically no effect on swelling (see Graph 5).

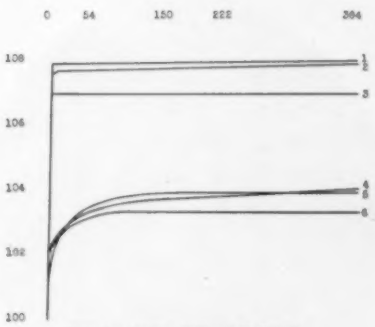
Ethylene glycol, diethylene glycol and carbitol cause about the same percentage swelling as water, except that water comes to equilibrium more rapidly. Dioxan and propylene glycol cause less swelling than alcohol but more than glycerin (see Graph 6).



Swelling of Chestnut Wood Blocks in Solvents.
Swelling Expressed on Basis of Original Thickness = 100.

Abscissa: Time in Hours.
Ordinates: Percentage Swelling or Shrinking Based on Dry = 100.

Graph 6.



Curve 1 - Aqueous NaOH - 0.01 Normal.
Curve 2 - Aqueous HCl - 0.01 Normal.
Curve 3 - Water
Curve 4 - Alcohol.
Curve 5 - Alcoholic HCl - 0.01 Normal.
Curve 6 - Alcoholic NaOH - 0.01 Normal.

Swelling of Chestnut Wood Blocks in Solvents.
Swelling Expressed on Basis of Original Thickness = 100.

Abscissa: Time in Hours.
Ordinates: Percentage Swelling or Shrinking Based on Dry = 100.

Graph 7.

The presence of 0.01*N* HCl and 0.01*N* NaOH in water slightly increases the swelling of blocks of chestnut wood; this slight difference was not observed in earlier experiments with strips, where individual differences are more pronounced. In alcohol, 0.01*N* NaOH caused a slight decrease in swelling (see Graph 7).

Comparative Swelling with Grain and across Grain.—It is a generally accepted fact that swelling is greater across grain than with the grain. An experiment was carried out to secure quantitative data on this point. Chestnut wood blocks of the same size used in the preceding experiment were placed in water and measurements of the length (with grain) and width (across grain) made at various time intervals. Measurements were made both at the edge and at the center of the blocks. The data, expressed on the basis: dry = 100, were as follows, the results being based on the average of 3 blocks.

TABLE XI.

Swelling.	Time in Hours. 0. Dry.	4.	13.	24.	36. Water.	72.	124.
Across grain (long way) edge	100	101.2	102.0	102.3	102.5	102.5	102.5
Across grain (long way) center	100	100.9	101.8	102.2	102.3	102.4	102.4
With grain (edge)	100	100.5	100.5	100.6	100.6	100.5	100.5
With grain (center)	100	100.6	100.6	100.5	100.6	100.6	100.6

The results show that swelling across grain is greater than with the grain. Swelling at the center and edge of the blocks is practically the same.

Photomicrographic Study of Swelling.—The chief kinds of tissues in chestnut wood are fibres, vessels and medullary rays. The structure is not uniform throughout, on account of the variations in growth at different seasons. Thus Plate 1 shows clearly the occurrence of spring wood, early summer wood and late summer wood.

Photomicrographs were made of sections of spring wood and summer wood cut from blocks which had been immersed for 4 months in water, alcohol, glycerin and the respective mixtures of these liquids used in the swelling and penetration tests. With water the cell walls appear filled out and under tension and the cavities appear fully opened. From the difference in appearance of the tissues in alcohol and in glycerin it seems that alcohol may cause less swelling than glycerin. With mixtures of equal volumes of glycerin and water and glycerin and alcohol, the cell walls appear to be completely swollen. Ternary mixtures of glycerin-alcohol-water which were used, produced much the same effects as water alone. Because of the variations in growth at different seasons there is a gradual change in the nature of the cells and it would not be safe to draw conclusions from fine measurements of cells from two different sections.

Plate 1.—A section cut from a block immersed in alcohol for four months, showing the different types of wood, namely, spring wood (large cells), early summer wood and late summer wood (adjacent to spring wood).

Due to inherent difficulties standing in the way of direct comparisons between different sections, a study was made of the effects of consecutive addition of different solvents to the same section. Since it was difficult to make thin sections of dry wood on the microtome, the procedure was adopted of obtaining sections from a block which had been immersed in alcohol for 4 months, the sections being air-dried for several days before use, during which time they apparently reverted to approximately the original condition.

Plate 2 shows the appearance of an air-dried section of summer wood, and the appearance of the same section after successive treatment with alcohol (2 hours), water (1 hour) and glycerin (6 hours). By identifying certain cells and thus measuring the same cells after treatment with different liquids, the following measurements were obtained from the photomicrographs, using a reading glass and a metric scale, and expressing the results in mm. Below are given the averages of the results.

	Air-Dried.	Alcohol.	Water.	Glycerin.
Across cavities	1.75	2.40	2.75	2.85
Between cavities (across double cell wall)	2.60	2.90	4.15	4.35
Between medullary rays	36	38	40	42

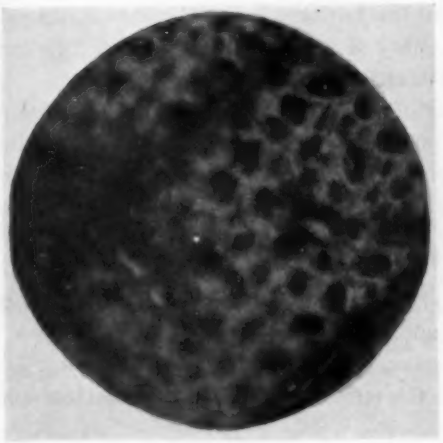


Fig. 1.

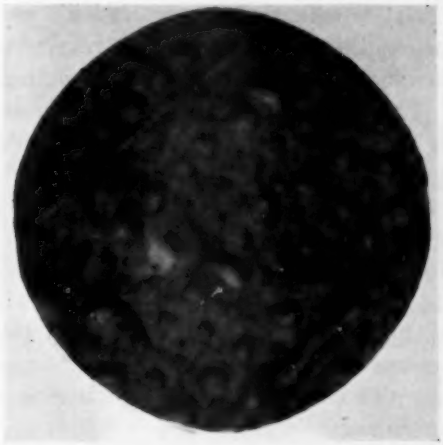


Fig. 2.

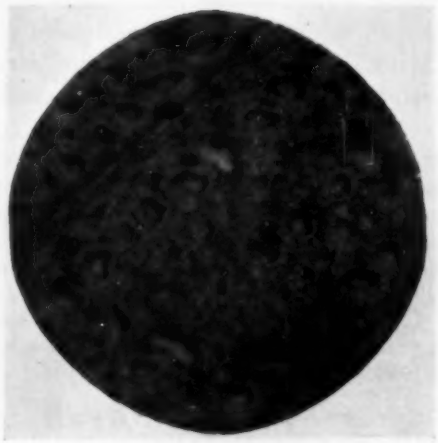


Fig. 3.

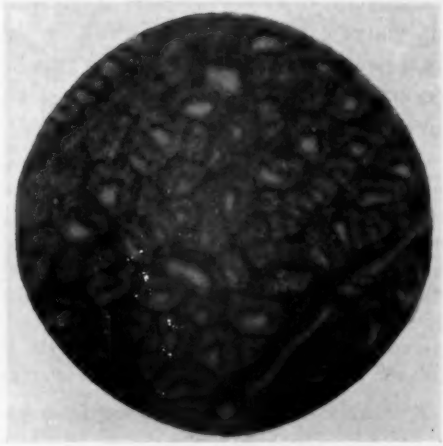


Fig. 4.

Photomicrographs of Chestnut Summer Wood.

Plate 2.—A section cut from a block immersed in alcohol for four months was air-dried (Fig. 1), and treated consecutively with alcohol (Fig. 2), water (Fig. 3) and glycerin (Fig. 4).

Thus it is seen that alcohol swells both the walls and cavities of the air-dried wood, both of which are enlarged by the successive addition of water and further slightly enlarged by glycerin.

Photomicrographs were also prepared to show the successive treatment of an air-dried section with (*a*) water, alcohol and glycerin, (*b*) glycerin and water, (*c*) glycerin and alcohol.

Below are given the averages of measurements taken from photomicrographs of an air-dried section of summer wood, treated consecutively with water (1 hour), alcohol (2 hours) and glycerin (6 hours).

	Air-Dried.	Water.	Alcohol.	Glycerin.
Across cavities	1.65	2.00	2.00	2.25
Between cavities (across double cell wall)	3.85	5.30	4.75	5.15
Between medullary rays	34	38	36	37

It is seen that water causes a swelling of both walls and cavities; alcohol shrinks the walls but does not reverse the effect of water on the cavities; glycerin then increases the size of both the walls and cavities.

Measurements were made between medullary rays in photomicrographs of an air-dried section treated with glycerin (6 hours) and then with water (12 hours), and are as follows: air-dried 16 mm.; glycerin 17 mm.; water 18 mm. Glycerin is thus shown to cause swelling. There is a further swelling with water, which may be due to a more complete penetration by glycerin, since the addition of glycerin after water (Plate 2) caused an increase.

An air-dried section was treated with glycerin (6 hours) and then with alcohol (12 hours). The distance between two medullary rays in photomicrographs of sections are as follows: air-dried 29 mm.; glycerin 33 mm.; alcohol 31 mm. It is thus seen that glycerin causes swelling and the subsequent treatment with alcohol caused some shrinking.

Discussion of Results.—In general, the results bear out the previous conclusions obtained on blocks and strips of chestnut wood, *i. e.* that alcohol causes some swelling, water causes a greater swelling than alcohol, while glycerin causes about the same swelling as water, although this effect is not shown when glycerin (undiluted) acts on dry wood, due to the very slow penetration by glycerin under these conditions.

Swelling of Blocks of Other Woods.—Tests were made on blocks of fresh oak sapwood of the water oak, Quercus nigra, 1. (Fagaceæ), in three conditions, namely, (*a*) fresh, (*b*) dried to constant weight at room temperature and (*c*) dried to constant weight at 90° C. in an oven. The blocks were about 25 mm. square, about 5 mm. thick (across grain) and averaged about 3 Gm. in weight. Using 3 blocks to each solvent, blocks were immersed in water, alcohol and glycerin in bottles placed in a thermostat at 30° C. After various intervals the blocks were removed and measured. The results of the swelling tests are given in the following tables, the figures in each case being based on the average of 3 blocks.

TABLE XII.—SWELLING OF FRESH OAK SAPWOOD BLOCKS IN LIQUIDS.
(Dimensions of blocks stated on basis: dry = 100.)

Time in Hours.	0.	3.	22.	46.	96.	528.	912.	1536.
				(Thickness—across grain)				
Water	100	100.0	100.0	100.0	100.0	100.1	100.1	100.1
Alcohol	100	100.0	100.0	99.9	99.8	99.9	99.9	99.9
Glycerin	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0
				(Width—across grain)				
Water	100	100.0	100.0	100.0	100.0	100.1	100.1	100.1
Alcohol	100	100.0	100.0	100.0	100.1	100.2	100.3	100.3
Glycerin	100	100.0	100.0	100.0	100.0	100.2	100.2	100.2
				(Length—with grain)				
Water	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Alcohol	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Glycerin	100	100.0	100.0	100.0	100.0	100.1	100.1	100.1

The blocks of fresh sapwood of oak are apparently in a state of maximum size, inasmuch as there is practically no swelling in any of the three dimensions in water, alcohol or glycerin.

TABLE XIII.—LOSS IN SIZE OF BLOCKS OF FRESH OAK SAPWOOD ON DRYING.

Time in Hours.	0.	3.	22.	46.	96.	528.	912.	1536.
				(Thickness—across grain)				
Room temp.	100	99.8	97.4	95.5	94.5	94.5	94.0	94.0
At 90° C.	100	98.4	95.7	92.3	92.2	92.2	92.1	92.1
				(Width—across grain)				
Room temp.	100	99.8	95.8	90.7	89.2	88.9	88.8	88.8
At 90° C.	100	94.0	90.2	85.4	85.4	85.2	85.1	85.1
				(Length—with grain)				
Room temp.	100	100.0	99.9	99.7	99.7	99.7	99.7	99.7
At 90° C.	100	99.9	99.7	99.7	99.7	99.7	99.6	99.6

The loss in size of the blocks, as shown in the table, occurs chiefly across the grain and is greater in the samples dried in the oven at 90° C. than in the ones dried at room temperature. It is strikingly shown that there is only a negligible shrinking with the grain on drying.

TABLE XIV.—SWELLING IN LIQUIDS OF OAK SAPWOOD BLOCKS DRIED AT ROOM TEMPERATURE.

Time in Hours.	0.	3.	10.	24.	72.	240.	720.
(Dimensions of blocks stated on basis: dimensions of fresh blocks *before drying* = 100.)							
				(Thickness—across grain)			
Water	94.7	99.1	99.2	99.6	99.6	99.6	99.6
Alcohol	93.2	99.0	99.0	99.0	99.0	99.0	99.0
Glycerin	95.1	94.9	94.7	94.7	94.7	94.8	95.7
				(Width—across grain)			
Water	89.4	95.2	98.8	99.2	99.4	99.4	99.5
Alcohol	88.6	97.3	97.4	97.5	97.5	97.6	97.7
Glycerin	88.5	88.1	88.3	88.4	89.6	91.7	93.7
				(Length—with grain)			
Water	99.7	100.1	100.2	100.2	100.2	100.2	100.2
Alcohol	99.6	99.9	99.9	100.0	100.0	100.0	100.0
Glycerin	99.6	99.7	99.7	99.7	99.7	99.9	100.0

TABLE XV.—SWELLING IN LIQUIDS OF OAK SAPWOOD BLOCKS DRIED IN OVEN AT 90° C.

Time in Hours.	0.	3.	10.	24.	72.	240.	720.
(Dimensions of blocks stated on basis: dimensions of fresh blocks *before drying* = 100.)							
				(Thickness—across grain)			
Water	92.8	96.1	98.2	98.4	98.6	98.7	98.8
Alcohol	91.4	94.6	95.2	95.8	96.1	96.3	96.4
Glycerin	92.0	92.0	92.0	92.1	92.1	92.1	92.8
				(Width—across grain)			
Water	84.4	90.9	95.9	96.6	97.1	97.6	97.8
Alcohol	86.5	94.9	95.1	95.5	95.8	96.0	96.0
Glycerin	84.5	85.0	85.0	85.0	85.0	85.2	85.8
				(Length—with grain)			
Water	99.6	99.9	100.0	100.1	100.1	100.2	100.2
Alcohol	99.5	99.8	99.8	99.8	99.9	100.0	100.0
Glycerin	99.8	100.0	100.0	100.0	100.0	100.0	100.0

The dried blocks when immersed in liquids recover the slight decrease in length which occurred on drying, and the shrinkage across grain is reversed almost completely by water, less by alcohol and still less by glycerin.

Results similar to those obtained on the effect of liquids on oak sapwood have been obtained on blocks of Elberta peach wood and on blocks of the sapwood of Sassafras variifolium (Salisbury) O. Kuntz (Lauraceæ). (*To be continued.*)

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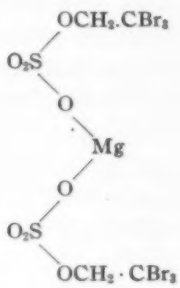
MAGNESIUM SALT OF TRIBROMETHYL SULPHURIC ACID.*

BY E. MONESS AND W. G. CHRISTIANSEN.

As part of a research on rectal anesthetics we became interested in determining whether or not the anesthetic properties of magnesium sulphate and polyhalogen aliphatic compounds could be combined in a single, water-soluble compound. Polyhalogen compounds such as ethyl chloride, methylene chloride and chloroform are inhalation anesthetics and tribrom ethanol is a rectal anesthetic. It seemed

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.

possible that the magnesium salt of tribromethyl sulphuric acid (I) might be a useful, water-soluble, rectal anesthetic.



The acid ester was prepared by reacting tribromethanol with fuming sulphuric acid in the cold. It was then converted into the magnesium salt. This salt was water-soluble but its activity as a rectal anesthetic was about one-eighth of that of tribromomethanol, *i. e.*, approximately eight times the quantity of this salt, as compared with tribromoethanol, were required to produce rectal analgesia.

The tests were made using 5%, 10%, 15% and 20% aqueous solutions of the salts and injecting a constant volume (25 cc./Kg.) into rats. Results were entirely negative with the 5% and 10% solutions. The 15% solution (dose 3.75 Gm./Kg.) produced a weakened ataxic condition which persisted up to the time the animal was sacrificed four hours later. The rat to which the 20% solution was administered failed to respond to tail pinching 55 minutes after dosage. This analgesic condition, with marked and continually increasing weakness, persisted from then until the animal died 35 minutes later. This behavior indicates that the compound cannot be advantageously used as a rectal anesthetic.

EXPERIMENTAL.

Preparation of the Magnesium Salt of the Acid Sulphate of Tribromethanol ($CBr_3.CH_2.OSO_3$)$_2$-*Mg.*—The method is an adaptation of the one disclosed in German Patent 7278, December 31, 1893, for the preparation of sodium amyl sulphate.

4.2 Gm. of tribromethanol was placed in a small test-tube and to it was added 1.5 Gm. of concentrated sulphuric acid. The viscous solution was cooled in an ice-salt bath and 2 Gm. of 60% fuming sulphuric acid was added from a small burette—one drop at a time, stirring with a thermometer, and not permitting the temperature to rise above 0° C.—about 25 minutes were required. After about half of the fuming sulphuric acid had been added, the reaction mixture became semi-solid. It was allowed to come to room temperature and poured into crushed ice and water. The excess sulphuric acid was precipitated with a solution of a slight excess of $Ba(OH)_2$ and the barium sulphate was filtered off. The excess barium hydroxide in the filtrate was then precipitated with a solution of magnesium sulphate, the precipitate filtered off and the filtrate evaporated to dryness *in vacuo* at a temperature of 50° C. The residue was now extracted twice with absolute alcohol, and the extract evaporated to a small volume by the addition of a large volume of ether. The compound was precipitated from this solution as a white crystalline salt, which was washed with ether by decantation and dried *in vacuo*. Yield—2.2 Gm. of a water-soluble and alcohol-soluble salt.

Analysis.	Found.	Calculated for ($C_3H_2Br_3SO_4$)$_2$Mg.
Br	58.4%	64.2%
Mg	4.72%	3.25%
S	9.06%	8.55%

The analysis shows that our compound was contaminated with a small amount of $MgSO_4$, but this was held not to interfere with the tests for rectal anesthesia.

The compound, when heated for a long time at 100° C. decomposes with the liberation of HBr, and the formation of water and alcohol-insoluble substance.

The biological tests on compounds reported herein were made in the biological Research Laboratories of E R. Squibb and Sons and we gratefully acknowledge their assistance.

RESEARCH DEPARTMENT OF THE CHEMICAL
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A METHOD FOR THE PREPARATION OF PARENTERAL DEXTROSE SOLUTIONS.

BY HARVEY A. K. WHITNEY.*

As a first premise it may be stated that a solution of dextrose suitable for parenteral administration may be made from a simple solution of chemically pure dextrose in chemically pure water. This statement is made with due consideration for the arguments for and against such factors as distilling apparatus, water, dextrose, hydrogen-ion concentration, buffers, preservatives and glassware. These modifying factors must be given consideration and together with the following elements, introduced at the time of administration, such as infusion apparatus, temperature of solution, velocity of injection and individual idiosyncrasy serve to complicate the apparently simple procedure issued as the original premise.

Distilling apparatus should be of a design that incorporates the following desirable and necessary features. Preferably the entrance of the raw water to the boiling chamber should be through condensers, permitting a preheating of the raw water, and venting the consequent discharge of many volatile substances. The insertion of a spray-trap or baffle-plates is also requisite to prevent the mechanical carry-over of boiling water or wet steam into the distillate. And lastly, the final delivery of the pure dry steam into vented condensers that will permit, if necessary, the delivery of the distillate into a closed system. It is pertinent to add that the whole interior of the distilling system should be lined with block tin.

Water obtained from the apparatus described, and under the circumstances necessary for the proper operation of the still, will provide a suitable solvent that may be used for the preparation of Aqua Destillata Sterilisata, U. S. P. Water distilled within the working hours of the morning or afternoon should be collected and disposed in a sterilized container of insoluble glass. The containers should be stoppered and sterilized under steam pressure giving a temperature of 115° C. for thirty minutes. If an autoclave is not available, close the mouth of flask containing freshly distilled water with a plug of purified absorbent cotton wrapped in gauze, and boil contents actively for one hour. Until ready for use, protect the mouth of flask, and plug from infection through dust, by wrapping top of flask tightly with paper. Sterilized distilled water so prepared should be used within

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.

twenty-four hours after its distillation. That such water must be protected against microörganic contamination was definitely shown by Seibert (*Am. J. Physiol.*, 67 (1923), 90). The product described by her as "pyrogen" is held to be greatly responsible for post-infusion "bad" reactions. The observations of precautions enumerated by the United States Pharmacopœia are quite sufficient to prevent bacterial infection of water properly distilled.

Dextrose of no less a quality than that defined by the Pharmacopœia should be used. This provides definite limits for water content, ash, dextrin, lactose, soluble starch, sulphites, sulphates, chlorides, heavy metals and optical rotation. Under no circumstances should impure glucose (corn syrup) be employed in this work.

Hydrogen-ion concentration measurement of the simple dextrose solution reveals a figure that is probably never more acidic than p_H 5.0, after sterilization, unless excessive decomposition (caramelization) obtains. In general this measure of hydrogen-ion concentration is indicative of the degree of decomposition after sterilization. It should be further appreciated that this figure also discloses another significant fact in that *practically all available acidity is measured*. Such knowledge should tend to minimize the anticipated physiologic effect of using such dextrose solutions that are more acid than the blood. It may still be admitted, however, that in some extraordinary instances of excessive depletion of the alkali reserve, the extemporaneous addition of an alkali (buffer salts) at the time of administration may be discreet. For the reasons just mentioned it may be concluded that the routine use of buffer salts is to be depreciated.

Preservatives, generally, are not in use at the present time. The use of such materials was quite generally discussed and disposed of by the Council on Pharmacy and Chemistry of the A. M. A. Certainly the introduction of a preservative in this solution is to be regarded as an admission of lack of professional skill.

Glassware, unquestionably, should be uninfluential to the hydrogen-ion concentration and chemical balance of the solution it contains. To provide for this unchanging condition, the use of insoluble or alkali-free glass is advised. Our own experience with "hard" and "soft" glass has developed some interesting observations. It can well be imagined there are intermediate qualities of glass that make available qualities "harder" than "soft." At present we are using, with considerable satisfaction, such an electric-tempered "harder-than-soft" quality in the shape of a wide-mouth french-square bottle of forty-ounce capacity finished with a shallow continuous screw thread (G. C. A. 400) that permits the use of a special 48-mm. molded screw cap fitted with a packet liner. These bottles will contain one liter of solution with sufficient residual void. In use such bottles routinely receive a preliminary cleansing and subsequent processing generally in accord with the following routine. They are filled with a solution of boric acid, autoclaved, and the solution dispensed for surgical purposes. Upon return of the empty bottles to the pharmacy they are thoroughly washed, rinsed well with freshly distilled water, capped and dried and sterilized in a Lautenschlager-type sterilizer. They are then regarded as conditioned for use with dextrose solutions. Glassware in which the silicates (free-alkali) have been so fixed has proven itself suited for this particular use.

Rubber tubing, unless carefully selected introduces a factor active in the pro-

duction of untoward reactions. Only specially selected pure gum rubber tubing should be used for setting up the infusion apparatus. This tubing should be prepared for use, when new, by thoroughly washing in running tap water. Then soak, or better autoclave, in a 5% solution of sodium carbonate. Finally a rinse in running distilled water for another thirty minutes will provide a suitable tubing. After this preparation it may be wrapped in a towel and sterilized by autoclaving in the approved manner. It is further suggested that after the apparatus has been set up for an infusion it is always best to discard the first fraction of solution being administered that will completely fill the length of tubing used.

Solutions of dextrose in the distilled water should be brought about with all the pharmaceutical skill at one's command. We prefer to pass this solution through a Berkefeld filter, under pressure, more with the thought of clarifying the solution than of obtaining a sterile product. This solution is transferred into the containers described, capped and hooded with a parchment paper cap that protects the lip and neck of the bottle. This hermetically sealed package is placed in the autoclave and processed as described for Aqua Destillata Sterilisata, that is, sterilization is to be preferably accomplished under steam pressure giving a temperature of 115° C. and maintained for thirty minutes. It should be reiterated that a common fault of "soft" glassware, if not properly prepared, is that at this temperature discoloration as by caramelization may develop. Sample bottles are selected from each lot and tested chemically and bacteriologically. The finished solution for parenteral use is a clear, colorless, sterile, physiologically compatible solution. A printed label describing the solution as to composition and character, together with a control number identifying the batch, is then attached. Such solutions remain stable for a considerable time.

THE EXTEMPORANEOUS PREPARATION OF SALINE AND GLUCOSE SOLUTIONS FOR INTRAVENOUS USE.*

BY ROBERT S. FUQUA.[1]

The use of intravenous therapy by physicians and surgeons has been constantly increasing in late years, especially in hospital practice. While manufacturing pharmacists have done much to make intravenous medication safer and more convenient for the physician, it appears that most pharmacists outside the manufacturing field have been slow to accept responsibility for the extemporaneous preparation of suitable solutions for this form of medication. Since the need for much of the intravenous medication is largely of an emergency nature, the writer can think of no valid reason why the trained pharmacist, in either the hospital or retail field, should consider this work to be the sole responsibility of the large manufacturing laboratories.

As indicated in the title, this paper will discuss the preparation of only the two most frequently used solutions of this type—that of Physiological Saline Solution, or "Normal Salt," and the intravenous solutions of Dextrose. Such information regarding these as the writer has been able to obtain, has been gained

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* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.

[1] Chief Pharmacist, Johns Hopkins Hospital, Baltimore, Md.

over a period of years in the pharmacy department of one of the larger eastern hospitals, where large volumes of such solutions are prepared. This experience has shown that with proper care, close attention to details and a supply of pure materials, the well-trained pharmacist can, with a little practice, soon become proficient in the preparation of satisfactory intravenous solutions.

Regarding the materials required, it should be remembered that the standards of purity set up in our Pharmacopœia for some of these items are not established on the theory that all U. S. P. chemicals, and the distilled water used for pharmaceutical compounding, must be of sufficient purity for intravenous therapy. No super-judgment is required to determine those instances in which materials of a higher standard of purity than is necessary for oral medication should be used for this purpose. In the case of dextrose, it is perhaps unfortunate that we must have in the Pharmacopœia the impure mixture of dextrins, dextrose and levulose recognized under the title "Glucosum;" when physicans assume that medicinally the name Glucose applies only to the U. S. P. Dextrose, or D—Glucose. At this time however, it seems rather unlikely that any pharmacist would dispense the impure syrupy product when glucose is ordered by a physician for medicinal uses. For making intravenous solutions, the U. S. P. Dextrose, which usually contains traces of dextrin, and possibly sulphur dioxide, should not be used. Only the variety of glucose marketed by standard chemical manufacturers as "C.P. Anhydrous Dextrose" should be used. The processes employed in the dehydration and recrystallization of the latter product remove practically all traces of the above-named impurities, which may be present in the hydrated material.

In making Normal Salt Solution, I would not hesitate to use sodium chloride of U. S. P. purity specifications when a purer salt was not immediately available. However, we may, and do, use a C.P. or Reagent grade of sodium chloride to insure maximum purity in saline solution for intravenous administration. A point which I would like to stress here is that no chemical which has been freely exposed to contamination by dust and other atmospheric impurities should be used in solutions which are to be injected into the blood stream, regardless of indicated purity on label of container. This applies with even more force to the distilled water which is to be used as a solvent. The Pharmacopœia lists certain tests to which distilled water must conform to be satisfactory for ordinary pharmaceutical purposes. Here again, water which conforms to these mandatory requirements as to purity may fall short of that degree of purity needed to produce satisfactory intravenous solutions. Distilled water may pass all standard tests for chemical purity, and be more nearly neutral in reaction to hydrogen-ion indicators than is necessary to come within the p_H range of those specified in the U. S. P., and still be totally unfit for intravenous injection, because of bacterial contamination. The specifications set up for the "Sterilized Distilled Water" of the U. S. P. are in line with those generally held necessary for a suitable diluent for the sterile concentrated solutions supplied in ampuls by manufacturing laboratories, and for general hypodermic use. For the extemporaneous preparation of these solutions, which must be filtered and sterilized as final steps, we need freshly distilled water, which has been exposed to bacterial or other contamination as little as possible, but not necessarily sterilized before use. All distilled water contains traces of carbon dioxide and oxygen, which are absorbed when steam is condensed; and usually will

absorb more on standing in contact with air. We have found however, that the usual slight acidity in distilled water, when due entirely to small quantities of CO_2 in solution, is of small consequence as compared to the dangers incident to undue exposure of the fresh distillate to contaminated atmosphere.

Sterilization of solutions will kill all living bacteria which they contain, but will not remove the bacterial proteins and other related impurities which remain in the finished product. This fact is well known to all interested persons, but seems to be frequently overlooked. Perhaps we sometimes forget that the atmosphere in most places is loaded with bacteria and organisms of various sorts and that these furnish the proteins and other substances which produce most of the toxic symptoms observed when carelessly prepared intravenous solutions are used. Under no circumstances should distilled water which has been purchased in bulk containers, commercially, be used in preparing intravenous solutions, unless same has been redistilled immediately before use, and according to the Pharmacopœial process. Normal Salt Solution which has not been freshly prepared should likewise not be used as a solvent.

I would like to depart from subject in hand momentarily, to say that Normal Salt solution should never be kept on hand in pharmacies for use when same is ordered as a solvent in any preparation. We have had bacteriological tests made on such solutions which were made under aseptic conditions and stored in partly filled, cork-stoppered bottles, on prescription-counter shelves. After two weeks many colonies of bacteria appear in cultures; and after one month such solutions are dangerous to use in preparations for local use on membranous surfaces, or in the eye if same has been injured.

Regarding the process of making Normal Salt Solution for intravenous use, little need be said here. Our procedure calls for the use of water which has been distilled the same day as used, and protected as far as possible from atmospheric or other contamination before use. Solutions are now being filtered through a hard smooth-surfaced filter paper, in covered glass funnels, into a well-covered, glass-lined receptacle. When filtration is completed the finished solution is placed in flasks of suitable size, stoppered with a plug of non-absorbent cotton wrapped in close-meshed gauze, which has been previously flamed to remove adhering lint, capped with a strong paper cap which extends well down the neck of the flasks, and then sterilized. Our sterilizing technique calls for autoclaving this solution at 125° C. for a period of thirty minutes. In the retail establishment not having facilities for autoclaving, sterilization may be accomplished for immediate use by boiling the solution for an equal length of time, providing an excess of water sufficient to take care of evaporation is added when solution is made. Proper filtration of this solution appears to be the greatest problem encountered. A complete absence of filter shred in filtrate is impossible to obtain with the standard grades of pharmaceutical filter paper, especially those with creped surfaces. After a number of experiments we selected an extra-hard grade of smooth-surfaced paper as offering the most practical solution. Suction filtration through candle filters will give better results for a time, but on extended use these are not wholly satisfactory. For large-scale production we keep a battery of these on hand for use in case a faulty lot of filter paper is encountered.

In making intravenous glucose solutions we use freshly distilled water, col-

lected directly from the still in large glass flasks. The glucose is dissolved in this immediately, without heat, and solutions are filtered at once through chemically hardened filter paper, in Büchner type porcelain funnels, by means of vacuum suction, into flasks which have been thoroughly cleaned and rinsed. Solutions are refiltered if necessary to secure a properly cleaned filtrate. Filtered solutions which show only occasional isolated paper shreds are strained through sterile fine-meshed silk cloth to remove same, rather than risk further contamination in repeated filtrations. Small squares of silk cloth are kept on hand for this purpose, immersed in 70% alcohol. Filtration of solutions of dextrose is not difficult and vacuum-suction is not necessary when the softer grades of filter paper are used. It should be noted, however, that only those grades of filter paper which are free from starch and chlorine should be employed in the filtration of solutions for either hypodermic or intravenous use. More shreds will usually be found in filtrates when non-parchmentized papers are used, but these shreds can be removed if a silk cloth of very fine mesh is available for straining. Silk bolting cloth (200 mesh per inch) is very satisfactory for this purpose, but is rather expensive. These solutions are placed in flasks of proper size, stoppered and capped in the same manner as described for saline solution, and sterilized the same day as made. After cooling, the flasks of sterile glucose solution are placed in low-temperature refrigerators to prevent possible fermentation before use. Our routine age limit for the use of these sterile solutions, prepared and stored as indicated, is five days. Bacteriological tests have shown them to remain sterile in the flasks for a much longer period, but the shorter time limit is placed as a safety precaution. Sterilization of glucose solutions is accomplished by autoclaving at 120° C. for fifteen minutes, with volume per flask being limited to not more than 600 cc. Flasks are placed on hardwood boards in sterilizers to protect bottoms of flasks from overheating on metal shelves. Solutions of 5 and 10 per cent strengths are turned out sterile and crystal clear under this treatment. If an autoclave is not available, glucose solutions may be rendered sterile for immediate use by heating on a water-bath, partially immersed in boiling water, for one hour. Depending on filtration through the usual type of candle filter to render glucose solutions sterile is not a safe procedure to follow.

Questions regarding the advisability of buffering solutions of dextrose which are to be administered intravenously are frequently brought up, and considerable disagreement exists among physicians on this point. At present the apparent consensus of opinion appears to regard the addition of buffer salts necessary in only a small percentage of cases. Under other methods of preparing and preserving solutions, or for prolonged continuous administration, buffering might render these solutions safer to use. In our institution several thousand gallons of intravenous glucose solutions are being used each year, and we seldom find it necessary to use buffer salts in same in order to secure satisfactory clinical results.

A second question, on which there appears to be no consensus of medical opinion, pertains to the necessity of using double or triple distilled water in intravenous solutions in order to obtain satisfactory results. No answer to this question which did not take into consideration the quality of raw water supply, type of distilling apparatus and other factors involved in individual cases, would be proper. With a raw water supply of good quality, and with efficient automatic distilling

apparatus, to the operation of which we devote some care, we have found multiple distillations unnecessary.

To sum up, I would say that if reactions are to be avoided in the use of these intravenous solutions, cleanliness and care in the preparation are necessary from start to finish. The chemicals used must be of a proper degree of purity, and must be kept free from contamination by dust and moisture. All utensils and apparatus used must be thoroughly cleaned, and then rinsed with freshly distilled water before being used. The distilled water and finished solutions must not be contaminated by undue exposure to dust and bacteria in the air. Sterilization will kill bacteria but does not remove them from solutions. The presence of excessive numbers of killed bacteria in solutions may cause reactions. Filtration and sterilization methods employed must be adapted to the particular product being handled; and suitable methods of preservation must be employed to protect unstable solutions packaged in containers which are not sealed. The use of chemical preservatives, in sufficient quantities to keep solutions sterile, is not permissible where large volumes of dilute solutions are to be administered intravenously.

STUDIES ON BISMUTH SUBSALICYLATE PREPARATIONS.*

BY WILLAIM F. REINDOLLAR.

One of the important recent developments in syphilotherapy is the treatment of that disease by intramuscular injections of suspensions of insoluble bismuth compounds in oil. This drug is alternated with the arsenicals in a course of treatment, thereby reducing the toxic effects, caused by prolonged administration of the latter, and at the same time preventing the spirochete from adjusting itself to the environment produced by either drug. The serious consequences that may follow injections beneath the skin of any product of inferior quality, together with the toxic effects that follow an overdose, make the control both of the qualitative and quantitative aspects of the product a matter of paramount importance.

Bismuth as a spirillicide has been said to be second to arsphenamine and superior to mercury. It is less toxic than either arsenic or mercury, dose for dose, and apparently exhibits no predilection for any particular organ. It is slowly absorbed and probably cumulative. Although numerous forms of this drug are employed we are concerned only with the official product, bismuth subsalicylate. This is described in the U. S. P. X as "a basic salt of varying chemical composition, which, when dried to constant weight at 100° C. yields upon ignition not less than 62% and not more than 66% of bismuth oxide."

In the venereal clinics of the Maryland State Health Department bismuth is administered as the subsalicylate in suspension in olive oil, the concentration being so adjusted that 0.1 Gm. metallic bismuth is received in 1 cc. of oil. The injection is made deep into the gluteal muscles of the upper outer quadrant of the buttock, alternating the right and left sides. For administrations of this type it is evident that a drug must not only contain the correct amount of active ingredient, but must exhibit certain physical and chemical properties, if it is to produce an opti-

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.

mum effect with a minimum irritation. In such a medicament the crystals must be small and uniform and readily suspended upon agitation. If the crystals are too large they will irritate the surrounding tissue producing fibrosus and induration. If they tend to clump they form irritating masses with the same effect. In either case absorption is materially interfered with. On the other hand if a uniform suspension cannot be obtained, it is impossible to withdraw a sample containing the proper dose of bismuth.

The examination of bismuth subsalicylate suspensions therefore consists of two types of analysis, chemical and microscopic. The former is a quantitative determination of bismuth as set forth in the official assay, the latter method is here described. The sample is thoroughly agitated to produce a uniform appearance of suspension, and a thin glass rod is used to secure a drop and transfer it to a slide. A cover glass is immediately placed on top of the drop of suspension and gently rotated and pressed until a thin uniform smear lies between the slide and the cover slip. These smears are then examined under a magnification of about 450 diameters. The number and size of clumped areas may serve as a basis for a system of grading such as is used for milk sediments, or permanent records may be made by taking photomicrographs.

Six samples, representing well-known brands that are offered to the physician in Maryland, were analyzed by the foregoing procedure. In every case the quantitative requirements for bismuth were met, however the microscopic fields varied considerably. One sample was superior to all the rest, four samples were given intermediate ratings, while still another was distinctly inferior. Thus the microscopic test demonstrates, that, in a group of bismuth subsalicylate preparations, all of which have essentially the same composition, and all of which meet the percentage requirements for active ingredient, there may still be a difference in quality and therapeutic efficacy based on physical properties of the suspended salt.

PROBLEMS IN DENTAL PHARMACY.*

BY A. O. MICKELSON.[1]

To understand the pharmaceutical needs of the dental profession, not including prescription writing, necessitates a thorough understanding of modern dentistry. The dentist's medicine cabinet for daily use and the pharmaceutical preparations and chemicals used in his laboratory work should be common knowledge to the pharmacist. The dentist is constantly using acids, alkalies, oxidizing agents, reducing agents, solvents, abrasives, hæmostatics, antiseptics, germicides, anesthetics—local and general, analgesics, sedatives, hypnotics and tonics.

A closer relationship between the two professions, discussing drugs or preparations used in dentistry, is undoubtedly the most effective way to understand the pharmaceutical needs of the dentist, and thus create new possibilities for professional pharmacy. The interview with the dentist should not cover a general scope, but instead study a specific problem, study the problem with the aim of solving his problem with him. Why should the pharmacist attempt to render

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1932.

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such a service to another profession? The answer is this: The pharmacist is the counselor to the allied medical professions and the more efficient and extensive this service becomes the greater will be the demand and remuneration for the pharmacist. In other words, the pharmacist must give professional service if he expects support from the correlated professions.

Quoting from the cover of the A. PH. A. JOURNAL, for February 1934, "Pharmacy Is Strengthened by That Which Makes It of Greater Service." A slogan on a publication by the Council on Dental Therapeutics, "We Serve Not for Ourselves but for Dentistry." This slogan may apply to any profession. The pharmacist is not serving the physician nor the dentist for the benefits to be derived for himself but for humanity, pharmacy and himself.

The method of individual contact, and choosing or developing a specific problem is the method I have found most helpful. The dental pharmacy problems are numerous—a new field full of possibilities. The scope of dental pharmacy is evidenced by the extensive work that is being done by the Council on Dental Therapeutics. The problem may require some coöperative research before it can be solved, but it is the solving of the technical and minute detail of a problem which give the most gratifying results. The field of dental pharmacy is most interesting and especially to the pharmacist interested in professional pharmacy.

The problems in Dental Pharmacy in this discussion have been suggested by personal contact with dentists. There is a need for a general massing fluid to be used for incorporating various types of abrasives which are used in prophylactic work. This massing fluid must possess the qualities of readily mixing with abrasives and with the desired amount of abrasive it should possess the quality of adhering sufficiently to the brush, rubber cup or whatever appliance may be used by the practitioner, as not to fly from the instrument as soon as the engine is in motion, throwing the abrasive powder on the clothing of the patient and the dentist. It should readily disintegrate in water, it should have a pleasing taste, as well as being antiseptic to prevent infection. During prophylactic treatment it is usual for the dentist to use more than one grade of abrasive. The massing fluid should serve for any abrasive desired.

The biggest problem confronting the dental profession is that of prescribing tonics which will build tooth structure in fetal life and in children, as well as tonics which will maintain tooth structure in permanent teeth. Such tonics in conjunction with food and vitamins are indeed not impossible. Considerable research work has been done by the dental profession, and favorable results have been reported in numerous cases. There is no question that the minerals such as calcium and phosphorus put up in proper combination are of extreme value to proper development of deciduous teeth and permanent teeth, as well as aiding materially in the prevention of decay of permanent teeth. It is evident that pharmacists can be most helpful in solving this problem.

There is a demand for a suitable formula, highly germicidal in action, for the sterilization of dental instruments. The sterilizing solution should be rapid in action, insuring complete sterilization in a few minutes' time without a corroding effect on the instruments. The solution should be reasonably safe to use and nontoxic to human tissue.

There are many individuals who fail to have their teeth cleaned and cared

for by the dentist at regular intervals, nor are they in the habit of using a tooth brush. Under these conditions dense calcific deposit may form around the gum margins and on the teeth. This is very difficult to remove. A solvent which will penetrate and soften such densely glazed calcific deposits would be of use to the dental profession. It must be taken into consideration that a solvent which would dissolve calcific deposits would also have a chemical action on the enamel of the teeth. However, a preparation in the hands of a skilful dentist would not come in direct contact with the enamel of the teeth.

Dry-sockets are of common occurrence in the practice of dentistry, and at times very difficult to restore as well as most painful to the patient. Help the dentist in your community solve his need for a treatment for dry-sockets.

The problems in dental pharmacy are numerous. We can only begin to realize the growing demand for dental pharmacy when we consider a national tentative curriculum in dentistry which includes subjects relating to treatment and diagnosis of abnormal conditions of the oral cavity as follows: Bacteriology, Preventive (Hygiene), Physiological Chemistry, Materia Medica, Physiology, Pharmacodynamics, General Pathology, Oral Medicine (Pulp Canal), Oral Pathology, Prevention (Nutrition), Diagnosis, Anesthesia, Oral Surgery, Oral Medicine, Principles of Medicine.

A curriculum including subjects as those mentioned gives us a picture of future dentistry. The dental profession is aware of the importance of their specialized branch of medicine in the prevention of disease and restoration of the teeth. We must contribute our part to the advancing profession if we are to maintain our recognition as professional men serving the needs of the correlated medical professions.

A STUDY OF VEHICLES FOR MEDICINES.*

BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

VIII. THE GLYCYRRHIZA VEHICLES.

That glycyrrhiza is a valuable disguising agent may be gathered merely from the extensive usage of at least some of its preparations. In Professor Gathercoal's (1) report this is given as follows:

	Usage per 10,000 Rs.
Syrup of Glycyrrhiza, N. F.	14.8
Fluidextract of Glycyrrhiza, U. S. P.	11.2
Elixir of Glycyrrhiza, U. S. P.	2.6
Fluidglycerate of Glycyrrhiza, N. F.	0.0
Aqueous Elixir of Glycyrrhiza, N. F.	0.0

The remarkable validity of this verdict of the medical profession, as expressed by the relative frequency of use of these preparations, will become clear by the perusal of this study.

* From the Laboratory of Pharmacology, University of Illinois, College of Medicine.

THE DISGUISING OF SALTY TASTES.

Experiment 1.

(*a*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Syrup.
(*b*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Fluidextract of Glycyrrhiza 1 part, water 3 parts.
(*c*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Syrup of Glycyrrhiza.

Those who taste the resulting solutions would, we believe, be in favor of the syrup of glycyrrhiza (*1c*) solution. The bromide solution in syrup (*1a*) tastes more salty; and the saltiness lingers after the sweetness of the sugar has left the palate. The fluidextract (*1b*) gives but little sweetness when the liquid enters the mouth, so that the saltiness predominates at first. This is followed by a period of prolonged sweetness which outlasts the saltiness of the bromide. The Syrup of Glycyrrhiza combines the immediate sweetness of the sugar solution with the prolonged sweetness of the glycyrrhiza.

Experiment 2.

Ammonium chloride, 0.30 Gm. dissolved in 5 cc. each of the three different solvents as above, yields the same conclusion.

Experiment 3.

Potassium iodide, 0.30 Gm. dissolved in 5 cc. each of the above solvents, also verifies results obtained.

Conclusion: The Syrup of Glycyrrhiza is a better vehicle for halides (Experiments 1, 2 and 3) than is simple syrup or the Fluidextract of Glycyrrhiza.

COLLOIDALITY LESSENS TASTE SENSATION.

This disguising power of glycyrrhiza for saltiness appears to be more than a mere matter of sweetness because there seems to be less saltiness in the taste of, *e. g.*, the bromide glycyrrhiza preparations than in equivalent solutions not only in simple syrup, but also in such flavoring syrups as the Syrup of Raspberry and the Compound Syrup of Sarsaparilla. There is apparently a loss of saline ions as far as taste sensation is concerned; and we attempted, by means of numerous experiments, to determine the reason for this loss.

One's first guess might be that the colloid interfered with diffusion of the crystalloid. True, established theory does not support this assumption. We, nevertheless, performed diffusion experiments (using collodion and celloidin sacs) with methylene blue solution and conducted similar studies with bromide. Whenever a difference was noted, this could always be ascribed to a leaky diffusion membrane. We also studied the modification in the development of "Liesegang's rings" (2) produced by colloid; but likewise without sufficiently striking results. That merely a difference in the rate of diffusion could hardly be the cause for the difference in taste might also have been obvious from the fact that the taste sensation is experienced immediately, while diffusion is a relatively slow process, at least as far as enabling one to demonstrate a difference by the experiments carried out.

It may be that differences in surface tension might explain this interference with taste sensation. Or, possibly, it might be due to adsorption of the saline ions by the colloid: it being well known that, when colloid is present, it is most difficult to re-

move the last traces of salt ions by diffusion. No matter how the colloid acts, it is evident that *colloidality has disguising value.*

THE BEST SOLVENT IS THE BEST VEHICLE.

To test the disguising value of the Syrup of Glycyrrhiza as compared with the elixirs, we prepared the following solutions:

Experiment 4.

(*a*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Syrup of Glycyrrhiza.
(*b*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Elixir of Glycyrrhiza.
(*c*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Aqueous Elixir of Glycyrrhiza.
(*d*) Dissolve 0.5 Gm. of sodium bromide in 5 cc. of Aromatic Elixir.

We believe that again the verdict would be in favor of the Syrup of Glycyrrhiza as compared with all of the elixir preparations. The solution in Aqueous Elixir of Glycyrrhiza is less offensive than the solution in the Elixir of Glycyrrhiza and this is less offensive than the solution in the aromatic elixir. It will be found that the bromide solution in syrup (*1a*) is more pleasant than are any of the alcoholic solutions, even though they contain glycyrrhiza; and the salty taste becomes progressively more noticeable with increase in alcohol concentration. The probable explanation for the superiority of the aqueous over the alcoholic vehicle is to be found in the insolubility of sodium bromide in alcohol. Evidently the presence of alcohol in the elixir makes the latter a poorer solvent than the watery medium of the tongue and palate. It is well known that, when two different solvents compete for the same solute, the latter will rapidly enter the better solvent in greater proportion than the poorer solvent. We might imagine, therefore, that the saline is quickly drawn from the alcohol containing solution into the more congenial aqueous medium of the mucous membrane. The reason, probably, why the aqueous elixir of glycyrrhiza (containing less than 5% of alcohol) is so distinctly inferior in its disguising power for saline taste, lies in the relatively small proportion of glycyrrhiza contained in it. We, therefore, believe that *it is a mistake to use elixirs for the disguising of water-soluble alcohol-insoluble salines.* The relative disguising inefficiency of the aqueous elixir of glycyrrhiza as well as its very limited use justify the suggestion that it be deleted. On the basis of observations such as the above and numerous others, we believe to be justified in pronouncing that, other things being equal, *the best solvent is the best vehicle.* Conclusion: the taste of the bromide in elixir is more offensive than that of a solution of bromide in Syrup of Glycyrrhiza.

THE DISGUISING OF THE BITTER TASTE.

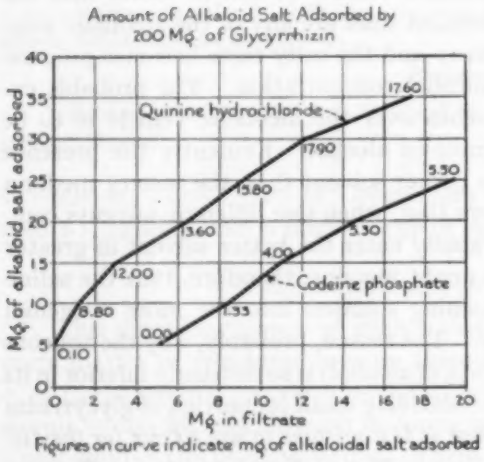
Experiment 5.

(*a*) Dissolve 0.025 Gm. of codeine phosphate in 5 cc. of Syrup.
(*b*) Dissolve 0.025 Gm. of codeine phosphate in 5 cc. of Syrup of Glycyrrhiza.
(*c*) Dissolve 0.025 Gm. of codeine phosphate in 5 cc. of Aromatic Syrup of Eriodictyon.
(*d*) Dissolve 0.025 Gm. of codeine phosphate in 5 cc. of Fluidextract of Glycyrrhiza and water, equal parts.
(*e*) Dissolve 0.025 Gm. of codeine phosphate in 5 cc. of Elixir of Glycyrrhiza.

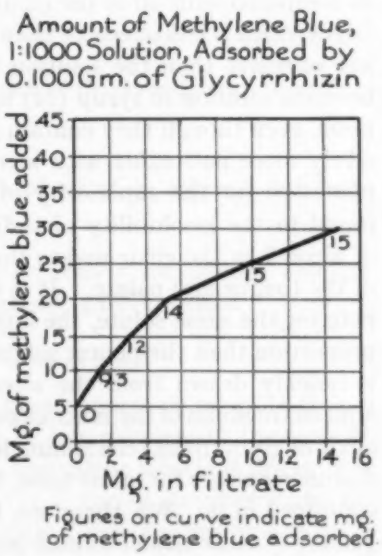
Again the solution in Syrup of Glycyrrhiza (*5b*) merits first place as far as palatability is concerned. The Aromatic Syrup of Eriodictyon probably comes next

in order of pleasantness; but it is quite evident that the amount of codeine phosphate (0.025 Gm.) exceeds the precipitating, hence the disguising power of the eriodictyon preparation. In a previous study (3) we have found that 5 cc. of the Aromatic Syrup of Eriodictyon were capable of disguising 0.008 Gm. of codeine phosphate. The subjoined Graph 1 gives the amount of codeine phosphate removed by glycyrrhizin from solutions of various strengths. It shows that the adsorption power of glycyrrhizin for codeine is rather limited and definitely less than that of the resin of eriodictyon (cf. 3). Nevertheless, its disguising power is obviously superior to that of eriodictyon, which must be due to the prolonged after sensation of sweetness produced by the glycyrrhizin, which is considered 150 times sweeter than sugar.

As to the removal of quinine from solution, adsorption experiments (Graph 1) show glycyrrhizin to be again decidedly inferior to the eriodictyon resin, as it also



Graph 1.



Graph 2.

is in regard to the adsorption of methylene blue from solution (Graph 2). This is likewise borne out by tasting experiments. Thus, a suspension of quinine ethyl carbonate (euquinine) in Syrup of Glycyrrhiza, while pleasant at first, becomes bitter soon thereafter and a prolonged bitter aftertaste is left. Similarly, one-fourth or one-half mg. of strychnine sulphate added to Syrup of Glycyrrhiza, while pleasant at first, leaves a lingering bitter aftertaste. We must conclude, therefore, that the Syrup of Glycyrrhiza is inferior to the Aromatic Syrup of Eriodictyon for the disguising of the bitter taste of alkaloids. Neither glycyrrhiza nor eriodictyon are of any value for the disguising of the bitter taste of aloin.

THE DISGUISING OF THE ALKALINE TASTE.

Experiment 6.

Dissolve (*a*) 0.60 Gm. of potassium carbonate in 0.3 cc. of water and add 5 cc. of Syrup.
(*b*) Repeat above and add Syrup of Glycyrrhiza instead of the Syrup.
(*c*) Repeat above and add Aromatic Syrup of Eriodictyon instead of the Syrup.

Again the Syrup of Glycyrrhiza gives the most pleasant disguise.

THE DISGUISING OF THE SOUR TASTE.

For the disguising of the sour taste glycyrrhiza is, of course, unsuitable, as the glycyrrhizin is precipitated by acid.

VARIABILITY OF GLYCYRRHIZA PREPARATIONS.

In view of the great disguising value of glycyrrhiza, the well-known variability of its preparations seems most unfortunate. It is common experience, in their prescribing, that some patients like the medicine, while others complain of its "nastiness." That this is not due to taste idiosyncrasies of individuals, but to variability of the glycyrrhiza preparations, is suggested by the fact that patients sometimes complain the medicine tasted differently on refilling, as though the druggist "had made a mistake." Our studies show that there is actually an enormous difference between the palatability of supposedly equivalent preparations bought in the open market, as well as between preparations made in our laboratory by identical methods from different samples of the drug.

TASTES OF VARIOUS SPECIMENS OF FLUIDEXTRACT OF GLYCYRRHIZA.

Specimen.	Prepared.	Taste.
1	In Laboratory	Sweet, slightly bitter
2	In Laboratory	Sweet, quite bitter
3	By Firm No. 1	Bitter, slightly sweet
4	By Firm No. 2	Bitter-sweet
5	By Firm No. 3	Bitterish and flavor of scorching
6	By Firm No. 4	Sweet, slightly bitter

Analogous differences were found in the Syrups of Glycyrrhiza made from these fluidextracts.

SYRUP OF GLYCYRRHIZIN.

The great variability of the glycyrrhiza preparations and the generally acknowledged difficulty of standardizing them, seems to us so serious an obstacle to their use as flavoring vehicles, that we undertook a great deal of experimentation with the view of discovering a method that would always yield a uniformly pleasant product. We started these experiments with the active principle, glycyrrhizin. The proportion of glycyrrhizin in glycyrrhiza is very variable, ranging from 6–14%. No wonder, we thought, there is such variation in the taste of the glycyrrhiza products. When we realize that, in addition to this, the sweetness of glycyrrhiza depends to a great extent upon the relative proportion of alkali metal, such as potassium, calcium or ammonium, with which the glycyrrhizin is associated, we can readily appreciate a reason for the difference in the taste of various specimens of rhizome from different sources as well as when they are kept in different ways. It seems that some specimens of rhizome have undergone an actual souring from improper preservation. We have found that the glycyrrhizin itself in such rhizomes is not changed, for though separated from even the bitterest fluidextract or rhizome, it is still capable of yielding a perfectly sweet product by combination with the proper amount of alkali. Inasmuch as glycyrrhiza contains about 3% of a bitter principle, which is certainly undesirable in a vehicle intended to disguise a

bitter taste, it seemed quite logical to prepare the Syrup of Glycyrrhiza from the active principle, just as we no longer prepare syrup by extracting and evaporating beet juice or sugar cane juice.

We found that the ammoniated glycyrrhizin is not as pleasantly sweet nor as colloidal as a more acid combination, *i. e.*, one containing a smaller relative proportion of ammonium hydroxide. After experimenting with various proportions of glycyrrhizin and diluted ammonia water, the best results were secured by a proportion of 1 part of glycyrrhizin to 4.5 parts of $N/10$ ammonium hydroxide. This yields so colloidal a liquid that a syrup made with 1% of the glycyrrhizin thus prepared becomes gelatinous. Owing to this high degree of colloidality we cannot employ more than $^1/_2$% of the glycyrrhizin in this combination. This is from $^1/_3$ to $^1/_7$ the amount of glycyrrhizin in its native, less colloidal state in the syrup made from the fluidextract. And yet this syrup of glycyrrhizin is quite efficient in the disguising of salines. This might serve as another proof of the idea, previously expressed, that it is the colloidality upon which the disguising power of these preparations for salines partly depends.

We employed the following formula for the preparation of the syrup of glycyrrhizin:

SYRUP OF GLYCYRRHIZIN.

Glycyrrhizin	**5.0 Gm.**
$N/10$ Ammonium Hydroxide Volumetric Solution	**22.5 cc.**
Distilled Water	**40.0 cc.**
Syrup, a sufficient quantity	
To make	**1000.0 cc.**

Triturate the glycyrrhizin with the distilled water and, while actively triturating, add the $N/10$ ammonium hydroxide and triturate until solution is effected. Then add enough of the syrup to make 1000 cc. and mix thoroughly.

At first thought this formula might be criticized as too expensive for consideration, owing to the high market price of glycyrrhizin, which is quoted at $4.40 a pound, or let us say, at about one cent per Gm. This would, however, make the glycyrrhizin cost five cents per 1000 cc. of the syrup, as against over sixty cents for the fluidextract or seventy cents for the fluidglycerate, which shows that the syrup of glycyrrhizin actually costs one-twelfth as much as far as the glycyrrhiza addition is concerned. Inasmuch as glycyrrhizin could not be secured in the market, we prepared it either from the ammoniated glycyrrhizin or, what is much more economic, from the drug itself. For this purpose, a concentrated aqueous percolate is acidified with hydrochloric acid. The precipitate is washed by repeated decantation until free from chloride ions, as indicated by Silver Nitrate T.S., and dried at moderate temperature.

Unfortunately, the Syrup of Glycyrrhizin is so colloidal that it is "salted out" by the addition of bromide, which makes it turbid immediately and causes a deflocculation of the glycyrrhizin on standing. We have not yet succeeded in determining what it is that keeps the glycyrrhizin from deflocculation when saline is added to a preparation made from the fluidextract. Inasmuch as ammoniated glycyrrhizin, which is less colloidal, is also deflocculated, there is probably another reason than a difference in the relative proportion of glycyrrhizin and alkali. We attempted to discover what it was in the extractives that kept from defloccula-

tion the glycyrrhizin in the syrup of glycyrrhiza, by adding the residue left after separation of the glycyrrhizin from extract of glycyrrhiza. This, however, failed to stabilize the preparation. It must be that the protective principle is denatured by the acid used in the separation of the glycyrrhizin.

We believe that the syrup of glycyrrhizin has decided merit and that it might ultimately replace the cruder product, providing it can be suitably stabilized. Owing to the advanced state of development of the forthcoming U. S. P. and the N. F. revisions, we desire to have the privilege, which we also grant freely to others, to make further observations with syrup of glycyrrhizin before advocating introduction of a formula for it in one of our official books.

AN IMPROVED FLUIDEXTRACT OF GLYCYRRHIZA.

In the present state of the glycyrrhiza situation, it seems that we must concentrate our efforts upon minimizing the nastiness and the variability of the glycyrrhiza preparation from which the Syrup of Glycyrrhiza is to be made. It is, in point of fact, being prepared from the fluidextract now, even though the N. F. specifies that it be made from the fluidglycerate. The reason we believe this to be the case is that the fluidglycerate is not kept in drug stores; that, indeed, it is not even upon the market; and that manufacturers had to prepare it specially for us when we insisted upon ordering it. As the specimens of fluidglycerate are just as variable as are those of the fluidextract, it presents no advantage from this standpoint; and furthermore it does not keep as well. For these reasons, and especially on the basis of non-use we propose that the fluidglycerate be deleted from the National Formulary.

It seems that the standardization of the Fluidextract of Glycyrrhiza from the standpoint of glycyrrhizin assay presents considerable difficulty as may be gathered from the literature on the subject (4–11). The simple methods are unreliable and the reliable methods, complicated. Nevertheless, it should be easily possible to lessen the variability of the preparation, at least as far as the content of solid extractive is concerned. This in preparations we have tested ranged between 20 and 30 per cent, as is shown by Table I.

TABLE I.—PERCENTAGE OF SOLID EXTRACT AND OF GLYCYRRHIZIN IN VARIOUS SPECIMENS OF FLUIDEXTRACT OF GLYCYRRHIZA.

	Per Cent of Solid Extract.	Per Cent of Glycyrrhizin in Extract.	Per Cent of Glycyrrhizin in Fluidextract.
Specimen 1	30	24.6	7.38
Specimen 2	27	24.2	6.54
Specimen 3	26	19.5	5.09
Specimen 4	25.7	23.1	5.94
Specimen 5	20	24.9	4.98
Specimen 6	23	..	..
Specimen 7	25.4	..	..
	Av. 25.3		Av. 5.98

NOTE: We were unable to determine the amount of solid extract in two other commercial samples because they failed to dry after heating for five days. The same difficulty was experienced with a fluidextract prepared in our laboratory by the U. S. P. IX method, in which ammonia water was employed.

It will be noted from Table I that, even though the amount of solid extract varied from 20 to 30 per cent, the average was practically 25 per cent. It is of interest to note that the amount of glycyrrhizin present was in four of the instances exactly one-fourth the quantity of the dry extract. For practical purposes, therefore, standardization in accordance with the amount of dry extract present in the fluidextract might suffice and the figure should be placed at 25 per cent.

There are two ways by which we might develop a fluidextract of Glycyrrhiza of standard solid extract content.

1. Exhaust the drug and concentrate the percolate to a somewhat greater extent than the ultimate bulk that the finished preparation is to have. By determining the quantity of the solid extract in a portion of the liquid thus obtained and adding enough fluid to bring the total solid residue content up to the standard, the desired result would be secured. What complicates the situation and makes the method just discussed unsuitable for the purpose is that the Fluidextract of Glycyrrhiza contains 25 per cent of alcohol and that the alcohol when added to the percolate produces a precipitate which is filtered out after sedimentation and decantation. The alcohol would either have to be added before the final concentration, in which case it would be difficult to secure a standard proportion of alcohol in the finished product, or else the alcohol would have to be added after standardization in which case it would render the previous determination invalid as the alcohol removes additional solid material from the preparation.

2. The other method would be to dissolve the pure extract of glycyrrhiza, which contains a variable quantity (about 25%) of moisture, in a certain quantity of water, an amount small enough so that the concentration will be excessive and dilution be required, adding the alcohol, separating the precipitate by sedimentation, decantation and filtration. Then the percentage of dry residue is determined in a small portion of the fluid, and the bulk is brought to the required amount to make the finished preparation carry 25 per cent of extractive by the addition of a sufficient quantity of a mixture of alcohol 1 part and water 3 parts. This is obviously the method to be chosen.

We, therefore, propose the following method for the preparation of the Fluidextract of Glycyrrhiza, which we would like to submit to the U. S. P. Revision Committee for consideration.

FLUIDEXTRACTUM GLYCYRRHIZÆ.

Fluidextract of Glycyrrhiza.

Fldext. Glycyrrh. Fluidextract of Licorice Root.

The Fluidextract of Glycyrrhiza contains not less than 24% and not more than 26% of dry extractive. The preparation should be of intensely sweet taste with but a slight tinge of bitterness, having the characteristic odor of glycyrrhiza and it should be free from even a suggestion of having become scorched in its preparation.

Extract of Glycyrrhiza, Pure ..... **400.0 Gm.**
Alcohol
Water, of each a sufficient quantity

Dissolve the pure extract of glycyrrhiza with the aid of the water-bath in enough water to make the solution measure 750 cc. Then add 250 cc. of alcohol and agitate the mixture. Set aside for 7 days, decant the clear liquid and filter the remainder. Determine the amount of solid extractive in 5 cc. of the liquid thus obtained by drying to constant weight. From the weight obtained calculate the number of grams per 100 cc. Calculate the quantity of solid extractive in the total quantity of liquid and add enough of a mixture of alcohol one part and water three parts to make the finished preparation contain exactly 25% of solid extract.

In explanation of the process advocated it might be pointed out that the extract of glycyrrhiza should contain 25% of moisture; but that it may contain more or less. In starting with an excess of the extract we save ourselves a preliminary determination of the dry extractive contained in it. When we dissolve 400.0 Gm.

of extract in 750 cc. of water, we are certain that dilution will be ultimately required, so that we may add 250 cc. of alcohol, confident that this will not be an excess, as the finished preparation will measure more than 1000 cc.

AN IMPROVED EXTRACT OF GLYCYRRHIZA.

We owe Dr. Percy A. Houseman the important information that the bitter principle of glycyrrhiza is extracted in much greater proportion toward the end of the percolation than in the beginning. Before having been apprised of this we made the observation, without realizing its significance, that when we tasted the first portions of a percolate we thought we would this time get a very palatable product; only to be bitterly disappointed by the bitterness of the final preparation.

When, for instance, we subject 200 Gm. of glycyrrhiza to percolation, according to the directions of the U. S. P.; but separate each successive 100-cc. portion, we secure fractions with a progressively decreasing amount of dry extractive in each as shown in Table II.

TABLE II.

Percolate.	Dry Extractive.	Taste.
100-cc. portion 1	8.2188 Gm.	Sweet
..... 2	9.3195 Gm.	"
..... 3	6.2855 Gm.	"
..... 4	5.0567 Gm.	"
..... 5	4.3387 Gm.	"
..... 6	4.3613 Gm.	Sweet, slightly acrid
..... 7	3.7498 Gm.	"
..... 8	2.7183 Gm.	"
..... 9	2.2088 Gm.	"
..... 10	1.8353 Gm.	Offensively acrid
..... 11	1.2655 Gm.	" worse
..... 12	0.8989 Gm.	"
..... 13	0.6730 Gm.	"
..... 14	0.5160 Gm.	"
250-cc. final portion	1.1152 Gm.	Bad
Total 1650 cc.	52.5613 Gm. =26.28%	

It will be noted that the first 500 cc. yield 33.2192 Gm. of extractive or 16.6%, which is 63% of the total extractive, and has a sweet taste devoid of acridity.

We, therefore, advocate consideration by the U. S. P. Revision Committee of the following formula for the Pure Extract of Glycyrrhiza.

EXTRACTUM GLYCYRRHIZÆ.

Pure Extract of Glycyrrhiza.

Ext. Glycyrrh. Pur. — Pure Extract of Licorice Root.

Glycyrrhiza, in coarse powder ..... 1000 Gm.
Boiling water, a sufficient quantity

Moisten the drug with boiling water, and macerate in a covered container in a warm place for two hours. Transfer the moist drug to a metal percolator (not iron) and percolate with boiling water until a yield of not over 150 Gm. of extract on a dry basis is obtained, which is likely to be secured in the first 2500 cc. of percolate. Evaporate this percolate promptly on a water-bath. Not over 200 Gm. of extract containing 25% moisture should be obtained.

ALTERNATIVE FORMULA FOR AN IMPROVED FLUIDEXTRACT OF GLYCYRRHIZA.

Should an alternative formula for the improved Fluidextract of Glycyrrhiza be desired in which the preparation is to be made from the crude drug, the following procedure might be considered.

FLUIDEXTRACT OF GLYCYRRHIZA.

Alternative Formula.

Glycyrrhiza, in coarse powder	**1000 Gm.**
Alcohol	
Water, a sufficient quantity	

Moisten the glycyrrhiza with 5000 cc. of boiling water, mix thoroughly, and allow it to macerate in a covered container in a warm place for two hours. Then transfer the moist drug to a tinned or enameled percolator, and allow the percolation to proceed, gradually adding boiling water until 2500 cc. are obtained. Evaporate the percolate on a water-bath or steam-bath to 300 cc. and when cold add 75 cc. of alcohol and mix thoroughly. Allow the product to stand for seven days in a stoppered container, then decant the clear liquid, filter the remainder, and wash the residue on the filter with a sufficient quantity of a mixture of alcohol 1 part and water 3 parts to make the fluidextract measure 400 cc.

Determine the amount of solid extractive in 5 cc. of the liquid thus obtained by drying to constant weight. From the amount obtained calculate the number of grams per 100 cc. Calculate the quantity of extractive in the total quantity of liquid and add enough of a mixture of alcohol 1 part and water 3 parts to make the finished preparation contain 25% of solid extract.

A "PALATABLE" SOLUTION OF CHLORAL HYDRATE.

The disguising value of the Fluidextract of Glycyrrhiza is illustrated by the following prescription which yields the least offensive liquid administration form of chloral hydrate that we are acquainted with.

℞	Chloral Hydrate	15.0 Gm.
	Gluside	0.06 Gm.
	Fluidextract of Glycyrrhiza	30.0 cc.
	Syrup of Orange, to make	60.0 cc.

M. and label: Teaspoonful in water at bedtime.

The addition of sodium bromide is admissible as shown by the following prescription:

℞	Chloral Hydrate	7.5 Gm.
	Sodium Bromide	15.0 Gm.
	Water	15.0 cc.
	Gluside	0.06 Gm.
	Fluidextract of Glycyrrhiza	30.0 cc.
	Syrup of Orange, to make	60.0 cc.

AROMATIC SYRUP OF GLYCYRRHIZA.

We deplore the crudeness of the formula for the Syrup of Glycyrrhiza at present official in the N. F. Not only is there no possibility whatever for the prescriber to know whether the patient will receive a moderately pleasant or a nasty preparation; but, even granted that the most palatable glycyrrhiza product is used, the mere addition of syrup to it does not yield as pleasant a preparation as could easily be secured by the use of a little flavoring. Every candy and chewing-gum manufacturer knows that the glycyrrhiza flavor needs to be improved by an anise bouquet. Our formulary does not make use of this knowledge. In experimenting to determine the most desirable flavor of glycyrrhiza, we find, after a trial of many

different formulas and proportions, that the anise flavor by itself is not sufficiently pleasing to be satisfactory. It is much improved by the addition of a suitable proportion of oil of fennel. If equal parts of oil of anise and oil of fennel are mixed, the anise flavor is almost completely overwhelmed by the fennel. The most acceptable proportion seems to be: 7 parts of oil of anise and 1 part of oil of fennel. Even this combination is not perfectly satisfactory. It has what might possibly be called a "musty" smell. In looking over formulas for anise bouquets, we find that this evidently is very generally recognized, for all such formulas contain some additional flavor, the function of which seems to be to add "liveliness" to the bouquet. We find oil of bitter almond, oil of spearmint and even nitrous ether used for this purpose. To us the bouquet of the N. F. Elixir of Anise seems to be the most desirable.

SYRUPUS GLYCYRRHIZÆ AROMATICUS.

Aromatic Syrup of Glycyrrhiza.

Syr. Glycyrrh. Arom.

Oil of Fennel	**0.05**	**cc.**
Anethol	**0.50**	**cc.**
Benzaldehyde	**0.015**	**cc.**
Fluidextract of Glycyrrhiza	**250**	**cc.**
Syrup, a sufficient quantity, to make	**1000**	**cc.**

Add the volatile oils to the Fluidextract of Glycyrrhiza and agitate until thoroughly mixed. Then add enough of syrup to make the product measure 1000 cc.

BROMIDE SYRUPS.

To the prescribing physician these studies yield the practical result that Syrup of Glycyrrhiza, especially in its improved form, the Aromatic Syrup of Glycyrrhiza, yields a palatable preparation, when used as vehicle for bromide. One might, therefore, suggest the following prescription.

℞	Sodium Bromide	30.0 Gm.
	Water, just enough for solution or	30.0 cc.
	Aromatic Syrup of Glycyrrhiza to make	120.0 cc.

M. and label: Teaspoonful in milk after meals and at bedtime.

A parenthetic note might not be amiss, in this connection, to explain the consideration underlying the second line of the above prescription. It is, of course, understood that the Syrup of Glycyrrhiza will not dissolve any considerable quantity of salt. It is also well known that syrups are relatively permanent only as long as they are saturated solutions. It is, therefore, necessary to add the minimal quantity of water that will dissolve the bromide so as to secure solution without dilution. The determination of this quantity might well be left to the pharmacist who if necessary can easily refresh his memory as to the solubilities by consulting his reference books, while it is hardly to be expected that the physician should carry these figures in his mind.

In this connection we would like to call attention to the joint responsibility of physician and pharmacist in the direction of delivering to the patient preparations that will keep without decomposition at ordinary room temperature. It happens not infrequently that a medicine that lasts for several days or more has undergone fermentation and become effervescing, even to the extent as to blow out the stopper.

Should this happen and the spoiled preparation be thrown away, it is even more fortunate than to have such a spoiled liquid forced down a child's unwilling throat, with possibly resultant digestive upset.

INCOMPATIBILITIES.

It might not be amiss at this point to recall to mind that glycyrrhiza has some of the following incompatibilities.

1. Acids, which precipitate the glycyrrhizin and destroy much of its sweetness.
2. Alkalies which destroy the colloidality of the preparation.
3. Heat which precipitates the glycyrrhizin.
4. Ionized iron compounds, because of resultant colloidal precipitate. Slightly ionized iron salts like iron and ammonium citrate may be added without precipitation.

CONCLUSIONS.

1. Glycyrrhiza is especially useful for the disguising of salines given in moderate dosage.

2. It is generally less efficient than eriodictyon for the disguising of the taste of alkaloids.

3. It is of but limited efficiency in the disguising of alkalies.

4. Its disguising power is due to the colloidality and the sweetening property of glycyrrhizin.

5. The Syrup of Glycyrrhiza is the most eligible of the glycyrrhiza preparations for disguising purposes in general.

6. The N. F. Syrup of Glycyrrhiza could be very much improved by an anise bouquet and we advise its introduction and the change of the title to "aromatic syrup of glycyrrhiza."

7. Owing to variability in the glycyrrhiza rhizome, which may result in a bitter instead of a sweet preparation, formulas for an improved Extract of Glycyrrhiza and Fluidextract of Glycyrrhiza have been elaborated, and are submitted for possible inclusion in the Pharmacopœia.

8. Other things being equal, the best solvent is the best vehicle. Hence it is an error to add alcohol to water-soluble, alcohol-insoluble saline, such as bromide. The taste of the bromide elixirs is more offensive than that of bromide syrups.

9. The Fluidglycerate of Glycyrrhiza should be deleted from the National Formulary, and also the Aqueous Elixir of Glycyrrhiza, as neither of them are employed to a sufficient extent to justify their retention.

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UNITED STATES PHARMACOPŒIA.

ABSTRACT OF PROPOSED CHANGES WITH NEW STANDARDS AND DESCRIPTIONS. ELEVENTH REVISION.

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PART I—INORGANIC CHEMICALS.

The Pharmacopœial Convention of 1930 recommended that "abstracts of changes proposed for the U. S. P. XI and new standards and descriptions" be published before final adoption, that those who are not members of the Revision Committee may have an opportunity for comment and criticism.

In compliance with this recommendation, the following abstracts are submitted. The nomenclature and the exact wording does not necessarily represent that to be finally adopted, and doses have not been appended.

Comments should be sent to the Chairman of the Revision Committee.

E. FULLERTON COOK,
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Philadelphia, Pa.

I. GENERAL TESTS.

1. Hydrogen-Ion Concentration.—A chapter on "Hydrogen Ions and p_H" has been prepared for inclusion in the section of the Pharmacopœia dealing with special tests. This monograph treats in a general way the theoretical considerations involved and sets forth in detail the colorimetric procedure for the determination of p_H. The colorimetric method has been adopted as the official procedure. However, owing to the fact that in many of the colored solutions of the Pharmacopœia this method is inapplicable, the potentiometric method is recognized as an alternative procedure. A table is included containing the salt-error corrections, and, also, suitable directions for the preparation of buffer solutions and indicator solutions accompany the chapter.

The advisability of incorporating a monograph of this kind into a modern pharmacopœia requires no defense. Precedent has already been established by the British Pharmacopœia of 1932, which has included such a monograph. The policy of Sub-Committee No. 7 in respect to the application of the principles of hydrogen-ion concentration to Pharmacopœial substances warrants comment. The Sub-Committee has not employed statements of p_H in the individual monographs for informative purposes only. If the information does not contribute to the tests for identity or purity, it has not been included in the official monograph. When, however, the information is useful as a means of identification or in establishing purity, the p_H of the substance has been included in the individual monograph. For the purposes of increasing stability and pharmaceutical elegance, p_H adjustment has been included in certain monographs.

In addition to the application of the foregoing policy of the Sub-Committee in respect to the individual monographs, an informative table setting forth the p_H of many of the official drugs in aqueous solution will be included in the section of "General Tests."

2. Electrolytic Determinations.—The U. S. P. X recognizes the electrolytic deposition methods as alternative analytical procedures for the determination of zinc, silver, mercury and copper salts. After much discussion and experimental work, the Sub-Committee decided to delete these electrolytic methods on the ground that the volumetric and gravimetric methods used to assay these salts were better suited for U. S. P. purposes than the electrolytic procedures.

3. Heavy Metals Test.—With certain minor modifications this test has been recommended for U. S. P. XI. After mixing the hydrogen sulphide T.S. and the liquid in question, the mixture is allowed to stand 10 minutes at room temperature instead of 30 minutes at 35° C. before examining for the appearance of a brown to black coloration.

4. Assay for Acids (Alkalimetric).—This general test has been deleted and more specific directions have been given under the individual acids.

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* Permission to reprint for purposes of comment can be had on application to the Chairman of the Board of Trustees, James H. Beal, Fort Walton, Fla.

5. Assay for Chlorides, Bromides and Iodides.—This general test has been deleted and more specific directions have been included under the individual salts.

6. Assay for Alkali Benzoates and Salicylates.—This general test has been deleted and special assays included for sodium benzoate and salicylate under the individual monographs. These assays depend upon the titration of the alkali bound to the organic acid with half-normal acid in the presence of a large amount of ether. Methyl orange T.S. is employed in the assay of sodium benzoate and Bromphenol Blue T.S. is used as the indicator in the assay of sodium salicylate. The precipitated organic acid is instantly dissolved in the ether by vigorous stirring and hence the vitiating of the end-point is obviated. This procedure with certain minor modifications is essentially the process employed in the British Pharmacopœia of 1932.

7. The Arsenic Test.—The arsenic test has been changed in many of its minor descriptive details. Throughout this revision an effort was made to harmonize the U. S. P. test with the arsenic test description and directions set forth in the Book of Methods of the Association of Official Agricultural Chemists 3rd Edition (1930), page 307.

Bettendorf's Arsenic Test has been deleted. This is recognized in the U. S. P. X for bismuth salts and antimony and potassium tartrate. It was observed that the general arsenic test was applicable to bismuth salts. Fleitmann's modification of the arsenic test has been included for antimony and potassium tartrate. The method depends upon the generation of hydrogen in alkaline medium; under this condition, arsine is formed but stibine is not formed. Hence antimony does not interfere in the test.

8. Turbidimetric and Clarity Tests.—Apparatus has been described and procedure outlined to determine the degree of turbidity in various preparations and solutions. The sample is matched against suspensions of fuller's earth (200 powder) in distilled water. Turbidities are expressed in parts per million. A description of the turbidimeter is given by J. R. Baylis, *Ind. Eng. Chem.*, 18 (1926), 311, and also Claman, Carr and Krantz, Jour. A. Ph. A., 21 (1932), 670.

II. GENERAL POLICIES.

1. Descriptive Matter in Monographs.—It was considered beyond the scope of the Pharmacopœia to include descriptive matter in the individual monographs which does not definitely contribute to the tests for identity or purity of the substances. These statements, some of them carried in the texts for three or four revisions, have been deleted. To illustrate this point with a specific case, the following statement in the U. S. P. X under Boric Acid has been deleted in its entirety:

"Heated to 100° C., Boric Acid loses water, forming metaboric acid (HBO_2) which slowly volatilizes at that temperature. Heated to about 160° C. Boric Acid fuses to a glassy mass of tetraboric or pyroboric acid ($H_2B_4O_7$). At about 185° C. the fused mass swells, loses all of its water, and becomes boron trioxide (B_2O_3), which fuses into a transparent non-volatile, hygroscopic mass."

2. Concentration of Diluted Acids.—The concentration of diluted acids is now based on a weight to weight percentage. For convenience in preparation, the concentration has been expressed on a weight to volume basis. Therefore, in the preparation of the diluted acids from the concentrated ones, the retail pharmacist need only measure a definite volume of the concentrated acid (corresponding to a definite weight) and make up to volume with distilled water.

3. Working Formulas.—Many working formulas for the preparation of inorganic chemicals have been deleted. It is believed that such substances as precipitated sulphur, exsiccated alum and granulated ferrous sulphate are not prepared by the small prescription counter methods any longer and, therefore, the recognition of these working formulas has outlived its usefulness.

III. INDIVIDUAL MONOGRAPHS.

1. Acidum Boricum.—The assay of boric acid has been modified by the addition of another 50 cc. of glycerin when the end-point of the titration is reached and then titrating further to the production of the pink color with phenolphthalein. Results obtained by this modified method are somewhat higher than those obtained by the U. S. P. X method and agree more closely with the theoretical value.

2. Acidum Hydriodicum Dilutum.—The working formula has been deleted. If this formula were retained, any sample of the acid which did not contain potassium acid tartrate, which remains as an impurity in the acid made by the official process, would be considered illegal. This view is taken owing to the ruling of the courts. The official definition contains also the statement: "Diluted Hydriodic Acid also contains not less than 0.6 Gm. or more than 1.0 Gm. of $H.H_2PO_2$ in 100 cc." An assay for the hypophosphorous acid content is included also in the monographs.

3. Acidum Hydrochloricum.—To conform with the concentration of commercial acids, the concentration has been changed from "31 to 33 per cent" to "35 to 38 per cent."

4. Acidum Nitricum.—To conform with the concentration of commercial acids, the concentration has been changed from "67 to 69 per cent" to "67 to 70 per cent."

5. Acidum Phosphoricum.—The argentimetric assay has been deleted. The alkalimetric assay using phenolphthalein as an indicator and saturating the titration mixture with sodium chloride is included. This assay is far more expeditious than the silver method and yields results sufficiently concordant for the purpose intended.

6. Acidum Sulphuricum.—To conform with the concentration of commercial acids, the concentration has been changed from "93 to 95 per cent" to "93 to 97 per cent."

7. Aqua.—A p_H range (5.6 to 8.3) has been included. The test for oxidizable substances has been deleted. This has been found to be unreliable when applied to various municipal-treated water supplies.

8. Aqua Destillata.—A p_H range (5.8 to 7.0) has been included. The test for oxidizable substances has been deleted.

9. Arsenii Iodidum.—This substance is assayed in the U. S. P. X argentimetrically. An oxidizing titration with tenth-normal iodine has been adopted. This conforms with the assay for arsenous oxide and determines the trivalent arsenic present.

10. Arseni Trioxidum.—The statement regarding the size of particles and physiological potency has been deleted.

11. Barii Sulphas.—The following "Bulkiness of Powder" test has been incorporated.

"Place 5 Gm. of Barium Sulphate, previously sifted through a No. 60 sieve, in a 50-cc. graduated cylinder provided with a glass stopper. The extent of the graduation of the cylinder should be about 14 cm. Add distilled water until a 50-cc. volume is obtained. Agitate the mixture briskly for exactly one minute and set it aside for sedimentation. Within fifteen minutes the Barium Sulphate should not settle below a volume of 12 cc. (bulkiness of powder)."

12. Calx.—Calcium oxide has been deleted and calcium hydroxide, for the preparation of lime water, has been included.

13. Calcii Bromidum.—The argentimetric assay has been deleted. The substance is directed to be assayed by the oxalate, permanganate method now employed for calcium carbonate.

14. Calcii Chloridum.—The argentimetric assay has been deleted. The substance is directed to be assayed by the oxalate, permanganate method now employed for calcium carbonate.

15. Carbonii Dioxidum.—Carbon dioxide of medicinal purity (99 per cent CO_2) has been admitted. The absence of carbon monoxide is required and an appropriate assay has been described.

16. Ferri et Ammonii Citras.—In the assay for iron in this substance a change in procedure has been adopted. Instead of allowing the hydrochloric acid solution of the sample to remain in contact with the potassium iodide for 30 minutes at 40° C., the titration of the iodine is begun without preliminary heating. The results obtained by this modification are practically identical with those obtained by the more lengthy process.

17. Liquor Ferri Chloridum.—The indigocarmine test for nitrate has been added to replace the ferrous sulphate test.

18. Liquor Hydrogenii Dioxidi.—The purity rubric has been changed from not less than 3 per cent to not less than 2.5 Gm. or more than 3.5 Gm. of H_2O_2 in each 100 cc.

19. Liquor Magnesii Citratis (Description and Assay).—Minor modifications of the assay have been included. The preliminary evaporation and carbonizing of the solution has been

omitted. A maximum and minimum magnesium oxide content will be incorporated. The (minimum total citric acid) test has been omitted. An identity test for citric acid has been included. An assay for the citric acid content has been included.

20. Liquor Potassii Arsenitis.—The maximum and minimum standards have been changed from 0.975 to 1.025 Gm. of As_2O_3 to 0.950 to 1.050 Gm. of As_2O_3 in each 100 cc.

21. Magma Magnesiæ.—The working formula has been omitted.

Methyl orange T.S. has been replaced by methyl red T.S. in the limit of soluble alkalies test.

The test for soluble salts and soluble alkalies has been modified.

Limits of heavy metals and arsenic have been included.

Limit of calcium test has been included.

22. Magnesii Carbonas.—The purity rubric has been changed from "not less than 39.2 per cent MgO" to not less than 40 per cent or more than 42 per cent MgO.

The limit of calcium oxide permitted to be present has been reduced from 0.8 per cent to 0.4 per cent. The cumbersome oxalate precipitation method employed for the determination of calcium has been replaced by a simple calcium sulphate precipitation procedure.

23. Magnesii Oxidum.—The limit of calcium oxide permitted to be present has been reduced from 2 per cent to 1 per cent.

The cumbersome oxalate precipitation method employed for the determination of calcium has been replaced by a simple calcium sulphate precipitation procedure.

24. Massa Ferri Carbonatis (Definition and Assay).—The purity rubric of not less than 35 per cent of $FeCO_3$ has been changed to not less than 36 per cent and not more than 41 per cent of $FeCO_3$.

Diphenylamine T.S. as an inside indicator in the assay has replaced potassium ferricyanide as an outside indicator.

25. Nitrogenii Monoxidum.—The following purity rubric has been incorporated: "Nitrogen Monoxide contains not less than 97 per cent by volume of N_2O."

A test for the absence of oxidizing impurities has been included. This test has been added to preclude the possibility of the higher oxides of nitrogen being present.

A detailed description of an assay has been added. This assay depends upon the differential solubility of N_2O in water contrasted with the solubilities of the generally occurring impurities.

26. Oxygenium.—The purity rubric has been increased from 98 per cent O by volume to 99 per cent O by volume.

A test to identify the presence of traces of carbon monoxide in oxygen has been developed. This test depends upon the reduction of iodine pentoxide and the detection of the liberated iodine. Description of the apparatus and a diagram accompanies the test. Carbon monoxide in concentrations of 1 to 100,000 are easily detectable by this method.

The assay has been described in complete detail. The alkaline pyrogallol absorption method has been replaced by the more easily manipulated ammonio-copper solution absorption method.

27. Pilulæ Ferri Carbonatis (Assay).—Diluted phosphoric acid has been used in place of diluted sulphuric acid for the solution of the pills.

Diphenylamine T.S. has been used as an inside indicator instead of potassium ferricyanide T.S. as an outside indicator, in the assay of these pills.

28. Potassii Carbonas.—The following test has been included to control the water content of the compound.

"Dry about 3 Gm. of Potassium carbonate, accurately weighed, to a constant weight at 180° C.: the loss is not less than 10 per cent or greater than 15 per cent (*water*)."

29. Potassii Hydroxidum.—In addition to sticks and fused masses, pellets and other forms of KOH have been recognized.

30. Potassii Iodidum.—The argentimetric assay has been deleted. The iodate direct titration method has been included. This latter method is specific for iodides and thus eliminates bromides and chlorides.

31. Sodii Benzoas.—The statement 1 Gm. of Sodium Benzoate is soluble in 61 cc. of alcohol at 25° C. has been changed to "1 Gm. is soluble in 50 cc. of a mixture of 47.5 cc. of alcohol and 3.7 cc. of distilled water at 25° C."

32. Sodii Biphosphas.—This salt is assayed argentimetrically in the U. S. P. X. As with phosphoric acid, this assay has been deleted and the alkalimetric procedure employed.

33. Sodii Hydroxidum.—In addition to the sticks and fused masses, pellets and other forms of NaOH have been recognized.

34. Sodii Iodidum.—The limit of water has been reduced from 7 per cent to 5 per cent.

The argentimetric assay has been deleted. The iodate direct titration method has been included. The latter method is specific for iodides and thus eliminates bromides and chlorides.

35. Sodii Nitris.—The assay has been made to conform with the assay of ethyl and amyl nitrites. This assay depends upon the liberation of iodine by the action of the nitrite on potassium iodide in the presence of sulphuric acid and the subsequent titration of the iodine with tenth-normal sodium thiosulphate solution in an atmosphere of carbon dioxide.

36. Sodii Phosphas.—In place of the efflorescent duodekahydrated sodium phosphate, the more stable heptahydrate has been recognized.

The official definition is:

"Sodium Phosphate when dried to a constant weight at 110° C. contains not less than 98 per cent of Na_2HPO_4. It contains not more than 50 per cent of water."

The argentimetric assay has been deleted and the more accurate magnesium pyrophosphate gravimetric procedure has been included.

37. Spiritus Ammoniæ Aromaticus (Definition and Assay).—The following definition has been included:

"Aromatic Spirit of Ammonia contains in each 100 cc. not less than 1.7 Gm. and not more than 2.1 Gm. of total ammonia and not less than 3.5 Gm. or more than 4.5 Gm. of normal ammonium carbonate $(NH_4)_2CO_3$."

The following assay has been included:

"*Total Ammonia.*—Measure accurately 10 cc. of Aromatic Spirit of Ammonia into a 200-cc. Erlenmeyer flask containing about 50 cc. of distilled water. Add 30 cc. of half-normal sulphuric acid and boil until the solution becomes clear. Cool and titrate the excess of acid with half-normal sodium hydroxide, using methyl red T.S. as an indicator. Each cc. of half-normal sulphuric acid corresponds to 0.0850 Gm. of NH_3."

"*Normal Ammonium Carbonate.*—Introduce another 10 cc. of the spirit, accurately measured, into a flask of about 300 cc. capacity. Add about 30 cc. of half-normal sodium hydroxide and boil this mixture, replacing the water lost by evaporation, until the vapors no longer turn moist, red litmus paper blue. Cool, add 6 drops of phenolphthalein T.S. and half-normal sulphuric acid until the color of the phenolphthalein is just discharged. Now add about 3 drops of methyl orange T.S. and titrate with half-normal sulphuric acid. Each cc. of half-normal sulphuric acid corresponds to 0.0480 Gm. of $(NH_4)_2CO_3$."

38. Tinctura Ferri Chloridi (Assay, Description and Definition).—The official definition has been changed to read.

"A hydro-alcoholic solution containing about 13 Gm. of ferric chloride ($FeCl_3$) in 100 cc., corresponding to not less than 4.5 Gm. per 100 cc. of Fe."

The indigocarmine test for nitrate has been added to replace the ferrous sulphate test.

The assay has been simplified according to the procedure set forth by Oakley and Krantz, Jour. A. Ph. A., 21 (1932), 468.

In the continual study and scrutiny of the monographs up until the time of publication, small changes in manipulation may be made and errors will be eliminated, but this survey contains the essential changes in the monographs reported.

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

Editor's Note: Could we confine our attention to the medicinals and preparations that are official in the U. S. P. and N. F., our teaching would be very much lightened. It is disappointing to the young graduate to go into a prescription pharmacy and find that a great deal that he had learned about U. S. P. and N. F. medicinals will be of little use to him because of the infrequent calls for them on prescriptions. There is no question but that it has become incumbent upon our colleges of pharmacy to give considerable attention to non-official medicinals if we wish our students to be successful in the prescription department. It is difficult to determine just how much time should be given to a study of these preparations. It is impossible to cover the total number thoroughly and the teacher must select for the purpose of study those that he thinks are most important. The following papers by Professors Andrews and Clark will be of interest to those who are confronted with this problem.—C. B. JORDAN, *Editor*.

THE PLACE OF SYNTHETICS AND PROPRIETARY REMEDIES IN THE CURRICULUM OF A COLLEGE OF PHARMACY.

BY A. H. CLARK.*

In the recent Prescription Ingredient Survey by Gathercoal, it is shown that about one-third of all the different items occurring in prescriptions are proprietary. When we consider that the average pharmacist sells many proprietaries that are never prescribed, it is safe to say that half the number of items sold are proprietary. If we add to this a number of items that are listed in the Survey mentioned above as U. S. P. or N. F. and which are really "synthetic" remedies, and the great number of synthetics that are used in hospitals and otherwise, and are not official in either the United States Pharmacopœia or National Formulary, the importance of a knowledge of these two classes of medicaments cannot be denied.

Granting, then, its importance, how can such a subject be best handled in a college of pharmacy? There are no doubt various ways that will prove satisfactory, and no doubt the method must vary with varying conditions in the different institutions. The writer wishes to express his views in the hope that some may have their interest stimulated to such a point that they will undertake to give instructions in this line, and that the manner in which the subject is handled by him may prove helpful to others.

The prime purpose of such a course should be to give the student an opportunity to acquire some knowledge of synthetic and proprietary remedies. There are two ways to attain this end, the first one being to discuss all such medicaments in the regular courses in organic chemistry where they fit in with the subject matter of such a course. Anything like a thorough treatment of proprietaries and synthetics greatly increases the hours devoted to the regular courses, which is objectionable in many cases. Such a method is impractical in some cases, since the regular courses in organic chemistry are given by teachers unfamiliar with the special pharmaceutical aspects of the subject. Furthermore, such a method does not

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sufficiently emphasize the subject of synthetics and proprietaries, and students fail to get an appreciation of its value and are unable to remember the desirable things because they are subordinated to the general topic of organic chemistry.

The second, and by far the most satisfactory method, is to present the subject in a special course, and here two lines of action are open. In either case the subject should be presented after the regular courses in organic chemistry are finished. One method is to group these medicaments according to their therapeutic action. The writer has tried this and while it is very acceptable to medical students it lacks many of the advantages of the method followed for many years which is given below.

These medicaments are classified according to their constitution, and arranged in groups, according to the system of grouping used by most organic texts. Since a student has a knowledge of the entire field of organic chemistry, both aliphatic and aromatic substances may be grouped together, for example *all* the aldehydes, acids, alcohols, etc., may be studied at once and their properties compared. If a medicament is heterogeneous in character, it may be placed in any one of several groups according to the teacher's best judgment. If it is a pharmaceutical mixture it may be treated under the group to which its most important constituent belongs. A great deal of latitude is allowed in this classification, as for example, chloral may be treated among the aldehydes, or the halogen derivatives, as may seem desirable. Barbiturates may be discussed under urea derivatives, or given a special class. Arsenicals may all be treated in one group, or the various types under their particular class. Very frequently a combination of chemical and therapeutic character is desirable as in the case of local anesthetics.

The writer has found the greatest advantage of this mode of treatment, regardless of the finer details upon which there is much room for differences of opinion, to lie in the fact that when it is given to senior students, it affords a most excellent method for review of the entire field of organic chemistry. By emphasizing the relationships of these medicaments to the various classes of organic substances, and the fact that their properties are usually due to the characteristic class structures present, the student must refresh his mind about these properties in order to see the connection. Finally, as time permits, there is no limit to the interesting discussions of the relationship between therapeutic activity and chemical constitution that may be introduced in a course arranged in this way, and there is no branch of chemistry that lends itself to the seminar system of instruction so well as this does, providing the class is not too large. There is no limit to the interesting discussions, investigations, reports, outside assignments of work, library reading, etc., that a small group can indulge in, if wisely directed by the instructor in charge of such a seminar.

METHOD OF APPROACH IN TEACHING THE PHARMACY OF NEW AND NON-OFFICIAL REMEDIES.

BY MARVIN J. ANDREWS.*

For the past several decades, it seems that the chemical and pharmaceutical manufacturers have been trying to surpass one another in the production of new

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remedies for nearly every disease from which mankind and other animals have been known to suffer. For want of a better term, we usually refer to these products as "new and non-official remedies." Some of these so-called remedies have but little merit and physicians soon cease to prescribe them. Others, which do have some real value as therapeutic agents, or are made to appear so through clever advertising, come into more or less general use. Whether these products belong to the first or second group, the dispenser must know something about their pharmacy if he is to intelligently fill the prescriptions calling for them. The method of approach to teaching this information to pharmacy students is the subject of this paper.

At the University of Maryland School of Pharmacy instruction to this end is given in three different departments, namely, the departments of Chemistry, Pharmacology and Pharmacy. This instruction is given primarily in the third year after the student has had the basic courses in chemistry, pharmacy and the biological sciences which are necessary for a proper understanding of the subject.

In the department of Chemistry, new and non-official remedies are considered along with the official products in a course entitled "Chemistry of Medicinal Products." This course is divided into two parts. One part deals with natural products, such as fatty oils, resins, carbohydrates, volatile oils, alkaloids, glycosides, enzymes, glandular products and vitamins; and the other part deals primarily with synthetics, such as the hypnotics, anesthetics, antipyretics, analgesics, pressor drugs, etc.

The department of Pharmacology limits the instruction which it gives covering these drugs and preparations to a consideration of their physiologic, pharmacologic, toxicologic and therapeutic properties. For purposes of study the drugs are grouped according to the physiological action which is of greatest therapeutic importance; methods of administration and dosage are emphasized.

In so far as the instruction in the pharmacy of these remedies is concerned, the approach is the same as that followed in giving instruction covering the official drugs and preparations. In our courses in pharmacy and dispensing, the more important of these remedies are covered in those cases where these products can be conveniently grouped with the official products. In attempting to do this, however, two main difficulties have been encountered. In the first place, these remedies are so numerous that it is difficult to determine their relative importance and to make a representative selection. In the second place it is often difficult, if not impossible, to obtain reliable information on the pharmacy of these remedies. We have attempted to overcome these difficulties by using some one of the various textbooks on new remedies, such as, "The Chemistry of Synthetic Drugs" by Percy May, or "New and Nonofficial Remedies" issued by the American Medical Association as a basis for the selection of the remedies to be covered. The time which can be devoted to instruction along these lines will not permit us to give consideration to more than a comparatively small number of these remedies. A few of the most widely used of these preparations are selected from each group as represented by similarity in chemical composition or in physiological action. Where information on the pharmacy of these products is not available in textbooks, we have searched through the journals for it and, in a few instances, we have conducted laboratory experiments to secure the desired information.

As previously stated, our method of approach to instruction to the students in

the pharmacy of these remedies does not differ from the method employed in teaching the official drugs and preparations. Our method of instructing students in dispensing may, however, have some points of interest for you.

The prescriptions containing the drugs and preparations to be studied are first classified into groups according to "New and Non-official Remedies," such as anesthetics, barbital compounds, silver preparations, etc., after which the students are assigned this chapter or group for study prior to the lecture and recitation. Whenever possible original packages of the material under discussion are shown the students during the lecture. An attempt is made to select preparations that have been previously studied in chemistry and pharmacology.

The prescriptions are placed in a baloptican projector and flashed on a silver screen in the front of the room in full view of the entire class. They are then read and discussed by the professor in charge during the first few lecture periods, or until the students become accustomed to the procedure, after which the students are called upon to read and discuss them.

In conclusion, the general procedure followed in the discussion of individual products may be summed up briefly by the use of the following example:

Name of Article	Luminal Sodium.
The Manufacturer	
Composition or Formula	The monosodium salt of phenylethylbarbituric acid. (All other information of this character is taken up in the department of chemistry.)
Description and Physical Properties	A white hygroscopic powder; very soluble in water; soluble in alcohol; practically insoluble in ether and chloroform. An aqueous solution of luminal-sodium has an alkaline reaction to litmus.
Actions and Uses	The same as those of phenolbarbital; sedative or hypnotic. (All other information of this character is taken up in the department of pharmacology.)
Dosage	1/2 to 5 grains.
Forms on the Market	Powder in 1/2- and 1-oz. bottles. Ampuls (powder) 2 and 5 grains. Capsules—5 grains. Tablets—1/4, 1/2 and 1 1/2 grains.
Incompatibilities	Is neutralized with free acid or acid solutions and the normal salt is precipitated in aqueous or low alcoholic solutions. (For example, Compound Elixir of Pepsin and Rennin, N. F., which contains free lactic acid.)

RESEARCH IN PHARMACEUTICAL EDUCATION.*

BY WILLIAM J. HUSA.[1]

The interest which pharmacists have in educational matters was evidenced many years ago by the establishment of this Section. Through the subsequent organization of the American Association of Colleges of Pharmacy and through the activities of the Committee on Educational Methods established by the National

* Section on Education and Legislation, A. PH. A., Washington meeting, 1934.

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Conference on Pharmaceutical Research further impetus has been given toward stimulating an interest in educational matters and building up a literature in this field.

Over the years a great deal of attention has been given to improvements in curricula and teaching methods and to various matters of educational technique such as types of examination, honors courses, etc. The interest in educational methods on the part of pharmacy teachers is very commendable, but there is one phase of pharmaceutical education whose paramount importance must never be lost sight of, *i. e.*, the correctness of the material that we teach. If the facts we are teaching are incorrect, or the explanations we offer are erroneous or highly improbable, of what avail are all the theories of educational procedure?

Lack of sufficient training on the part of the teacher of course leads directly to poor teaching. On one occasion in a court trial an instructor in a naval academy was questioned regarding his preparation in his field. In his reply he admitted that he was not well versed in the subject he was teaching, but stated that he endeavored to be a fair referee between the student and the book. In our field I recall the statement of a man who had had no training whatever in pharmacy, but who claimed that he could teach pharmacy, stating that if he got half a dozen pages ahead of the students they would never catch up with him.

However, in fields of wide scope, such as we have in the pharmaceutical sciences, in which changes are constantly occurring due to changes in medical practice and to the discovery of new facts in the underlying sciences, it is a real problem, even for the well-trained teacher, to keep his courses strictly up-to-date.

When teaching loads are heavy, and much time is required for routine clerical and committee work, and when a teacher is assigned to teach several branches in the field it becomes necessary to depend more and more on standard textbooks. In any case the mis-statements and discrepancies found in text and reference books are a hindrance to good teaching. In some instances such errors may be due to insufficient study of the literature on the part of the author. Frequently the error is due to discrepancies in the literature itself, and to differences of opinion which cannot be resolved without further research. Every pharmacy teacher should be constantly on the lookout for commonly accepted material which from his own special experience appears questionable. If he goes a step further and carries out literature studies and research work to determine which facts are correct, he is taking a great step toward improvement of his teaching. If he publishes his findings, thus making them generally available to his colleagues, he is making a definite contribution to pharmaceutical education.

By way of illustration, I will cite an example from my own experience. A few years ago I observed that contradictory statements appeared in various reference books regarding U. S. P. Benzoinated Lard. The supposed effect of benzoin in retarding the development of rancidity in lard was variously ascribed to the benzoic acid, cinnamic acid, volatile oil, resin and odorous constituents. This lack of agreement led me to make a search of the journal literature on this point; this showed many conflicting opinions but very little careful experimental work. With the assistance of co-workers, I have carried out several experimental studies to clear up this point. Our first work (1) showed that benzoic acid and cinnamic acids are not effective in retarding the rancidity of lard. Incidentally, a study of

other reputed preservatives was made (2); these were found ineffective with the exception of hydroquinone, which in concentration of 0.5% reduced the rate of development of rancidity about 50%. Although the value of benzoin as a preservative seemed well established in the older literature, some question arose on this point. We then found by experimentation (3) that plain lard deteriorated several times as rapidly as benzoinated lard. It was also found that benzoin was responsible for the change in color from white to gray which was observed in Ointment of Potassium Iodide, N. F. V. Finally the individual constituents of Siam benzoin were tested one by one and it was found that coniferyl benzoate is the constituent responsible for the preservative effect of Siam benzoin in lard (4). We thus have gained a satisfactory understanding of this preparation, which is official in a dozen of the leading pharmacopœias of the world.

The unsatisfactory statements in reference books regarding Solution of Arsenous and Mercuric Iodide, U. S. P. X led to studies which I will mention briefly in passing. Textbooks gave the impression that this solution contained a double compound of AsI_3 and HgI_2, while in reality it is a solution of arsenous acid, hydriodic acid and hydrogen mercuric iodide. A leading textbook stated that there was no chemical reaction in the making of this preparation, while as a matter of fact there are extensive chemical changes involving practically complete hydrolysis of the arsenous iodide and the formation of a complex ion. A leading reference book stated that the aqueous solution of arsenous iodide is neutral, whereas we found the p_H to be 1.2. By searching far enough back in the literature, we found that the acidity of the solution was known over a hundred years ago and this had repeatedly been verified by research workers since that time but these published researches were overlooked or disregarded by the "swivel-chair scientists" who made the pharmacopœias and other books.

It is logical that research for teaching should be done in our colleges. Some of the preparations which require study may derisively be called "antiquated solutions" or "stagecoach remedies" but as long as they remain official and must be included in our courses it is not to our credit to allow our knowledge and teaching to be inadequate and incorrect. No one teacher has the ability to find all such discrepancies or the time to study all that he might see, but if more such studies are made by more teachers it will be possible to eliminate a great deal of misinformation from our textbooks and place the teaching of pharmacy on a higher level.

REFERENCES.

(1) William J. Husa and Lydia M. Husa, Jour. A. Ph. A., 15 (1926), 1071–1074.
(2) William J. Husa and Lydia M. Husa, *Ibid.*, 17 (1928), 243–247.
(3) William J. Husa, *Ibid.*, 19 (1930), 825–828.
(4) William J. Husa and Donald E. Riley, *Ibid.*, 23 (1934), 54[illegible]-550.

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A REPORT ON INTER-PROFESSIONAL RELATIONSHIP WORK IN WISCONSIN.*

BY RALPH W. CLARK.[1]

During the time since the Madison meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION, two senior thesis students, Gerald Belisle and Wilbur Dehmer, a committee of the Wisconsin Pharmaceutical Association consisting of three physicians, three dentists and three pharmacists, and the writer have worked with some regularity on inter-professional relationship. To start the work, a meeting was held in Madison during the AMERICAN PHARMACEUTICAL ASSOCIATION convention in order to familiarize the members of the state committee with the national scope of the problem and the character of the work being done, by hearing Dr. Fantus and Dean Schicks speak on the physician and the dentist, respectively, in relation to the pharmacist.

The relationship between the physician and the pharmacist was discussed in a paper by the writer, Wilbur Dehmer coöperating, in the January *Wisconsin Druggist.* A full-page editorial in the *Wisconsin Medical Journal* for April commented favorably on this discussion and indicated the willingness of the physicians to coöperate. The writer has been asked to contribute to the latter magazine.

The relationship between the dentist and the pharmacist was presented in a paper by the writer, Gerald Belisle coöperating, in the April *Wisconsin Druggist.*

A meeting of the inter-professional relationship committee was held in Milwaukee in January at which Dr. Frank B. Kirby addressed the group. An informal discussion followed with druggists, physicians and dentists taking part. The members of the executive committee and the officers of the Wisconsin Pharmaceutical Association were present and physician and dentist members of the committee and guests.

An interesting program has been planned for the balance of the year. Rho Chi sponsors an annual open spring meeting at the University of Wisconsin. This year the meeting is to be turned into an inter-professional relationship discussion. Dr. Frank B. Kirby, M.D., director of Education of the Abbott Laboratories; H. P. Greeley, M.D., Madison, member of the editorial board of the *Wisconsin Medical Journal;* O. M. Dresen, D.D.S., Milwaukee, practicing dentist and member of the faculty of the Marquette Dental College; and Otto H. Berndt, president of the Wisconsin Pharmaceutical Association, will speak. A meeting of the executive committee of the Wisconsin Pharmaceutical Association has been called in Madison on May 22nd,[2] to bring these men to attend the Rho Chi gathering. University pharmacy students and local druggists, physicians and dentists are being invited. Displays of interest to physicians and dentists will be shown.

A portion of the Wisconsin Pharmaceutical Association convention program

* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1934.

[1] Instructor in Pharmacy, University of Wisconsin, Department of Pharmacy; Secretary, Wisconsin Pharmaceutical Association; Chairman, Committee on Inter-Professional Relationship of the Wisconsin Pharmaceutical Association.

[2] The meeting has been held, but the paper is printed to present this type of work. This meeting and similar ones he'd in other cities were well attended and were characterized by enthusiasm on the part of those present.—EDITOR.

is also to be given over to a similar discussion. Following the writer's report of his committee work, Dr. Kirby will speak. He will be followed by Dr. J. C. Sargent, M.D., Milwaukee, a member of the committee and Dr. Dresen, who has consented to appear on this program also. This part of the convention program was considered by many who attended, as one of the high spots of a paper read by the writer at the State Medical Society meeting on September 12th.

The above concludes the report of work done this year in Wisconsin on inter-professional relationship. The writer wishes to add a few comments which may provoke discussion.

The inter-professional relationship between physician and pharmacist has been a problem which has always occupied the minds of members of these professions. Pharmaceutical journals of both the popular and professional types, as well as medical journals, have devoted many pages to the subject. Recently, there has been a renewed and comprehensive attack on the relationship between these two kindred professions.

The inter-professional relationship between dentist and pharmacist, on the other hand, has been discussed only, comparatively, recently. Extensive work, in this field, has been done by George C. Shicks, Assistant Dean, Rutgers University, College of Pharmacy, and others since 1930.

Why not also include veterinarians? With the "back to horse" movement in farming territory, diseases and injuries to these as well as other domestic animals and pets call for medication which the small town druggist could and should prepare.

The writer believes that the real problem is to get the pharmacist to approach the physician or dentist in the proper way, knowing first that his own house is in order. This problem can be handled only by means of an educational campaign along these lines carried on in the pharmaceutical press. Recently, a great amount of material has been contributed pointing out methods of approach but neglecting emphasis on the fact that the pharmacist must put his own house in order, which includes discontinuing, to a large extent, counter prescribing and featuring of patent medicines and solving the problem of irregular prescription prices. Then, quoting Glenn Frank, "there is no reason why, as independent pharmacists, ... they should cease to be upstanding, independent factors in the economic life of this Commonwealth."

A serious obstacle to overcome is the fact that various pharmaceutical manufacturers detail physicians and dentists. Members of these professions would welcome a visit from their favorite pharmacist who could in this manner reduce the number of preparations prescribed and carried on his shelves. In the long run who would suffer? By and large, nobody. A certain pharmaceutical house might conceivably lose out in one case and gain in another.

In conclusion, the writer is of the opinion that although much can be done with this work by holding joint state and national meetings or as Dr. Kirby suggests, joint conventions with sections for the various professions; the real, final work must be done by and between individuals.

COMMITTEE REPORTS

REPORT OF THE FAIRCHILD SCHOLARSHIP COMMITTEE.

The Fairchild Scholarship Committee of last year was composed of Robert L. Swain, L. D. Havenhill, C. T. Gilbert and E. G. Eberle, Chairman. As the term of the three former officers terminated in May, the Chairman mailed the Fairchild Scholarship letters to these members. The Committee of this year is composed of Robert P. Fischelis, Ernest Little, C. H. Evans and E. G. Eberle, Chairman. The University of Notre Dame, School of Pharmacy, presented no candidate for the examination and the Head of the Department of Pharmacy, Dr. Lawrence H. Baldinger, with the assistance of other members of the faculty, consented to prepare the questions for the examination and grade the answers.

Twenty-nine candidates participated in the examination, representing nineteen schools

The examinations were given under three subjects: Pharmacy, Chemistry and Materia Medica. The highest general average was made in Pharmacy, 76.10; next in Materia Medica, 66.83; lowest, Chemistry, 54.17; general average, all subjects, 66.58. The highest per cent was made in Pharmacy, 92; next in Materia Medica, 91; next in Chemistry, 85. The lowest average was made in Chemistry, 28; next in Materia Medica, 49; next in Pharmacy, 56. The general average in Pharmacy was 76.10; sixteen made above that average; twenty-two made 70 or over. The general average in Materia Medica was 66.83, sixteen made above that average; fourteen made 70 or over. The general average in Chemistry was 54.17; eleven made above that average; four made 70 or over. The average of the general averages was 66.58; thirteen made above that average; ten made 70 or more.

Candidates of the same school did not have closely related records nor did the two candidates rank next to each other.

Scheduled report follows:

Candidate.	Pharmacy.	Chemistry.	Materia Medica.	Average.
1	86	85	91	87 1/3
2	83	83	76	80 2/3
3	80	79	76	78 1/3
4	92	76	60	76
5	88	58	81	75 2/3
6	78	63	84	75
7	86	67	71	74 1/3
8	78	61	82	73 2/3
9	89	50	77	72
10	67	69	75	70 1/3
11	76	53	79	69 1/3
12	80	55	69	68
13	70	52	79	67
14	76	54	68	66
15	84	46	68	66
16	74	57	61	64
17	79	47	66	64
18	75	46	70	63 1/3
19	84	52	55	63 1/3
20	75	53	60	62 2/3
21	87	40	59	62
22	72	47	66	61 2/3
23	82	38	62	60 2/3
24	67	34	75	58 1/3
25	56	46	71	57 2/3
26	63	43	65	57
27	58	51	49	52 1/3
28	62	38	57	52 1/3
29	60	28	62	50

The candidate making the highest record made a general average of 87 1/3 and the next in line made 80 2/3. The chairman of the Grading Committee, Lawrence H. Baldinger, Head of the Department of Pharmacy, University of Notre Dame, states: "The candidate who made the highest average wrote excellent papers in all of the subjects, papers which were consistent throughout. His marks were the highest in Chemistry and Materia Medica; in Pharmacy, however, he rated about sixth, but his paper was nevertheless very good."

The report of the Grading Committee was submitted to the members of both committees referred to at the beginning and all the members voted to accept the report of the Grading Committee.

The chairman desires to thank his colleagues for their support and the members of the Examining and Grading Committees for their helpfulness.

The winning candidate is Frederick F. Johnson, of the University of Washington College of Pharmacy; a sketch of the prize-winner follows.

E. G. EBERLE, *Chairman.*

SKETCH OF FAIRCHILD SCHOLAR, 1934.

Frederick F. Johnson was born in Seattle, Washington, May 17, 1912. He is a graduate of Roosevelt High School of Seattle and entered the University of Washington College of Pharmacy in September 1930. He received the degree of Bachelor of Science in Pharmacy in June 1934.

Mr. Johnson was admitted to associate membership in Sigma Xi on his scholarship record. He is a member of Rho Chi and was president of Rho chapter of Rho Chi during his senior year. He was elected to the honor roll of the Linton Memorial for 1934. This memorial, in the form of a plaque, was established by the local chapter of Kappa Psi fraternity in memory of the late Professor Arthur Linton. He is a member of Phi Sigma Kappa social fraternity. He was graduated with the rank of Ensign in the United States Naval Reserve after having spent four years in the Naval Reserve Training Corps of the University of Washington.

Mr. Johnson's avocation is music and his recreation is mountaineering. He will register in the graduate school of the University of Washington this autumn as a candidate for the degree of Master of Science in Pharmacy and expects to continue graduate study for the degree of Doctor of Philosophy.

The winner of the Fairchild Scholarship for 1934 is a son of Dean C. W. Johnson of the University of Washington College of Pharmacy.

F. F. JOHNSON.

PHARMACEUTICAL SERVICE IN THE BRITISH NAVY.

The Pharmaceutical Service consists of the following grades: (*a*) Head pharmacist; (*b*) superintending pharmacists; (*c*) senior pharmacists; (*d*) pharmacists. The age of pharmacists on entry must not be less than twenty-one nor more than twenty-eight years. Candidates must possess certificates that they hold either the Major or the Minor qualification of the Pharmaceutical Society of Great Britain or the certificate of competency granted by the Pharmaceutical Society of Ireland, and produce testimonials and a full record of training, qualifications and experience. Pharmacists will be paid a salary of £120 per annum on entry, rising by £7 10s. annually to £180.—From *Chemist and Druggist.*

CONFERENCE OF PHARMACEUTICAL LAW ENFORCEMENT OFFICIALS.

R. L. Swain, *Chairman*
2411 North Charles Street
Baltimore, Maryland

M. N. Ford, *Secy.-Treas.*
State Office Bldg.
Columbus, Ohio

TEMPORARY ABSENCE

under State Pharmacy Acts, as compiled by Chairman Swain.

Alabama.— . . . temporary absence as defined and prescribed by the Board of Pharmacy.

Arizona.—By temporary absence is meant only those unavoidable absences which may occur during the day's work, and when the registered pharmacist in charge shall be within immediate call, ready and able to assume the direct supervision of said pharmacy.

Arkansas.—No provision.

California.—Temporary absence within the meaning of this act, shall be held to be only those unavoidable absences which may occur during a day's work and when the registered pharmacist in charge shall be within immediate call, ready and able to assume direct supervision of said pharmacy.

Colorado.—Temporary absence means absence of not more than eight hours out of a sixteen-hour day, under the Rules and Regulations of the Colorado Board of Pharmacy.

Connecticut.—Provided for but not defined. By regulation of the Pharmacy Commission: If a Pharmacy is conducted with only one licensed pharmacist engaged therein and in charge thereof, and the absence of such licensed pharmacist from such store may become necessary for a greater period than one day, such pharmacist or the owner of such store, may make application to the commission for, and the commission may grant a leave of absence of such pharmacist for a reasonable temporary period greater than one day.

Delaware.—No provision.

District of Columbia.—No provision.

Florida.—No provision.

Georgia.—No provision.

Idaho.—The department of law enforcement may grant a permit to an assistant pharmacist for such time as the department may prescribe to conduct a drug store or pharmacy during the temporary absence of a regularly employed licensed pharmacist therein.

Illinois.—Any assistant pharmacist shall have the right to act as clerk or salesman in a drug store or pharmacy during the temporary absence of the registered pharmacist.

Indiana.—Temporary absence of a registered pharmacist shall be construed to mean that an assistant pharmacist may be left in personal charge of a registered pharmacy not more than two consecutive hours and not to exceed four hours in each twenty-four hours.

Iowa.—"Temporary absence" shall mean necessary absence for meals and business or other necessary causes while the pharmacy is open for business.

Kansas.—No provision.

Kentucky.—Registered assistant pharmacist may have charge of a drug store during the temporary absence of the registered pharmacist, but such absence shall not be for a longer period than thirty days in a calendar year.

Louisiana.—No report.

Maine.—But such store may be under the charge of a qualified assistant during the temporary absence of such registered apothecary. (Not otherwise defined.)

Maryland.—An assistant pharmacist shall not be left in charge of any pharmacy in this State for a period of more than twenty-four hours, and then acting only in the temporary absence of a registered pharmacist, regularly and continuously employed in that pharmacy.

Massachusetts.—No provision.

Michigan.—A registered assistant pharmacist may be employed . . . in any pharmacy or drug store . . . under the management and supervision of a registered pharmacist, and during his temporary absence therefrom. (Not otherwise defined.)

Minnesota.— . . . or during the temporary absence of such registered pharmacist, in charge of a registered assistant pharmacist. (Not otherwise defined.)

Mississippi.—No report.

Missouri.—No provision.

Montana.—No report.

Nebraska.—Temporary absence within the meaning of this act shall be held to be only those absences which may occur during a day's work, and when the registered pharmacist in charge shall be within immediate call, ready and able to assume the direct supervision of said pharmacy.

New Hampshire.—An assistant pharmacist may be left in charge of a pharmacy only during the temporary absence of a registered pharmacist, and such temporary absence shall in no case exceed forty-eight hours at any one time, nor fourteen days in any one calendar year, unless consent is obtained from the commission.

New Jersey.—The term "temporary absence" as used in this section shall mean an absence of not more than four hours in any one day of twenty-four hours.

New Mexico.—No provision.

New York.—A junior pharmacist may, subject to the rules of the Board, have temporary charge of a pharmacy or drug store, but during such temporary charge, shall not compound or dispense physicians' prescriptions.

North Carolina.—Provided, that during the temporary absence of the licensed pharmacist in charge of any pharmacy, drug store or chemical store, a licensed assistant pharmacist may conduct or have charge of said store.

The Board of Pharmacy of North Carolina gives the following interpretation: The term "temporary absence" in the Pharmacy Act shall be held to mean that interval during the period the store is open for business, when the registered manager is out of the store but within call and ready to assume direct supervision of said pharmacy.

The qualified assistant pharmacist may have charge of a retail drug store during such temporary absence of the registered pharmacist, and exercise his right to do what the law and his certificate confer upon him.

North Dakota.— . . . or during the temporary absence of such registered pharmacist, in charge of a registered assistant pharmacist.

Ohio.—No provision.

Oklahoma.— No provision.

Oregon.—Temporary absence, within the meaning of this act shall be held to be only those unavoidable absences which may occur during a day's work, and when the registered pharmacist in charge shall be within immediate call, ready and able to assume the direct supervision of said pharmacy.

Pennsylvania.—An assistant pharmacist . . . may also perform such duties during the temporary absence of the pharmacist regularly in charge.

Rhode Island.—No provision.

South Carolina.—The said Board shall make rules and regulations clearly defining temporary absence.

South Dakota.—Any registered assistant . . . may take charge of the drug store or pharmacy during the temporary absence of the manager thereof. Provided, that nothing in this section shall be construed as giving such assistant authority to perform continuously any of the duties herein mentioned, except under the supervision and in the presence of the manager.

Tennessee.—A registered assistant pharmacist shall have the right to fill prescriptions and dispense medicines in a drug store or pharmacy and during the temporary absence of the registered pharmacist in charge, provided such absence is not more than one-third of the time per week that the store is open for business.

Texas.—No provision.

Utah.—Temporary absence, within the meaning of this title, shall be held to be only those unavoidable absences which may occur during the day's work, not to exceed ten days and when the registered pharmacist in charge shall be within immediate call, ready and able to assume direct supervision of said pharmacy.

Vermont.—No provision.

Virginia.— . . . but during the temporary absence of such registered pharmacist, a registered assistant pharmacist may act in place of the said registered pharmacist. Board regu-

lations 2 (g): The term "temporary absence" as used in this act shall be construed to mean an absence from the pharmacy over which said registered pharmacist has personal supervision of less than one-half the hours that said pharmacy is open to the public for business.

Washington.—Ruling of the Director of Licenses: Temporary absence shall be held to be only those absences which may occur during a day's work, and when the registered pharmacist in charge shall be within immediate call ready and able to assume the direct supervision of said drug store or pharmacy.

West Virginia.—No provision.

Wisconsin.— . . . a registered assistant pharmacist . . . may have charge during the pharmacist's necessary absence, not to exceed ten days.

Wyoming.—No provision.

Office of the Secretary,
September 7, 1934.

CONFERENCE OF STATE ASSOCIATIONS IN MIDWEST.

The Midwest Conference of Pharmaceutical Associations was organized in Kansas City on September 3rd. Officials of five Midwest states—Iowa, Missouri, Nebraska, Oklahoma and Kansas—were present. The Colorado Pharmacal Association is expected to join the conference later, its officers being unable to attend this meeting. An organization was perfected, a Constitution and By-Laws adopted, officers elected and work started which is designed to be of benefit to the Independent Retail Druggists of these states.

Incorporated in the By-Laws is a clause which states the intent and purpose of the Conference. One purpose is to aid, assist and coöperate with the National Associations at all times for the mutual interest of independent druggists. Other purposes are to secure similar legislation in adjoining states and for the interchange of ideas and information valuable to the retail drug trade. The Conference adopted a resolution to request the N. A. R. D., at the New Orleans Convention, to approve and assist in organizing similar Conferences in other sections of the country. It is expected that this Conference will show a fairly militant spirit in its operations.

Officers elected were: *President*, John W. Slocum, Secretary of the Iowa Association; *Vice-President*, Guy Butler, President Nebraska Association; *Secretary-Treasurer*, Roy C. Reese, Secretary Kansas Association. Others attending the Conference were President Otto Bjornstad, Iowa Association; President Joe Knight, and Treasurer Murray Williams, Missouri Association; Secretary J. G. McBride, Nebraska Association; Secretary E. R. Weaver, Oklahoma Association; President Otto Kuether and Treasurer Walter H. Varnum, Kansas Association.

Future meetings are to be held quarterly.

ROY C. REESE, *Secretary-Treasurer.*

SECTION OF ILLINOIS PHARMACY LAW WITH REFERENCE TO SUBSTITUTION.

Section 14, Paragraph 2, of the Illinois Pharmacy Law provides as follows in regard to substitution:

"Nor shall any druggist or other person being requested by means of a prescription, or in any manner, to sell, furnish, or compound any drug, medicine, chemical or pharmaceutical preparation, substitute or cause to be substituted therefor, without notification to the purchaser, any other drug, medicine, chemical or pharmaceutical preparation. Any person violating any provision of this section upon conviction shall be liable to all the costs of the action and all the expenses incurred by the State Board of Pharmacy in connection therewith, and for the first offense shall be fined not less than ten dollars nor more than one hundred dollars, and for each subsequent offense shall be fined not less than seventy-five dollars nor more than one hundred and fifty dollars. The State Board of Pharmacy is hereby empowered to employ an analyst or chemist expert, whose duty it shall be to examine into any claimed adulteration, substitution or alteration, or other violation hereof, and report upon the result of his investigation, and, if such report justify such action, the board shall cause the offender to be prosecuted."

Substitution of the sort covered by the state law is now a violation of the Retail Drug Code under the NRA and subject to action by the Code Authority—Editor, C. R. D. A. News.

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1934–1935.

Office of the Secretary, 2215 Constitution Avenue, Washington, D. C.

LETTER NO. 4.

August 28, 1934.

To the Members of the Council:

24. Local Secretary for 1934–1935. Dean A. O. Mickelsen of Portland is recommended for election as Local Secretary by those who have charge of arrangements for the 1935 meeting in Portland. Dean Mickelsen is nominated as Local Secretary by E. F. Kelly. If members of the Council desire to submit other nominations, it is requested that these be forwarded promptly in order that a vote may be called for as early as possible.

25. Headquarters for the 1935 Meeting. The local committee who have charge of arrangements for the meeting recommend that the Hotel Multnomah be chosen as headquarters. This hotel is located at Fourth and Pine Streets, has eight stories, is a Class A fireproof, steel structure with 500 rooms, all outside, 400 of which have private baths or showers. The hotel has garage service and has submitted the following rates:

Room without bath—1 person	$1.75, 2.25, 3.00.
Room without bath—2 persons	$2.25, 2.75, 3.50.
Room with bath—1 person	$2.50, 3.00, 4.00, 5.00, 6.00.
Room with bath—2 persons	$3.50, 4.00, 5.00, 6.00, 8.00.
Room with bath—Twin beds	$5.00, 6.00, 8.00, 10.00.
Suites—Parlor, bedroom and bath	$10.00, 12.00.
Parlor, bedroom and bath, twin beds	$12.00, 14.00, 16.00.
PARTY BUSINESS, 10 or more—	
Single with bath	$2.50.
Double with bath	$3.50 to $6.00.
Twin beds with bath	$5.00 to $7.00.
MAIN DINING ROOM, table d'hote, luncheon 65¢ to $1.00, also a la carte. Dinner $1.00 to $1.50.	
COFFEE SHOP, table d'hote and a la carte service at moderate prices.	

Dean Mickelsen has forwarded a plan of the mezzanine floor of this Hotel which shows ample accommodations as to meeting rooms, all on one floor, and so arranged that they can be easily located.

26. Time of the 1935 Meeting. The local committee recommends that the meeting be held either the week of August 5th or of August 12th and states that the average temperature for Portland on these dates is 67°. The suggested dates were submitted to Secretary Christensen of the N. A. B. P. and to Chairman Jordan of the A. A. C. P. Secretary Christensen approved either date. Chairman Jordan expressed satisfaction that the meeting is to be held earlier and the opinion that the week of August 12th would be more satisfactory because a number of schools and colleges of pharmacy hold summer sessions and it would be difficult for their representatives to reach Portland for the earlier date.

Dean Jordan's statement was referred to Dean Mickelsen for consideration. In the meantime the Oregon and Washington Pharmaceutical Associations have decided to hold their annual meetings for 1935 in Portland on Monday and Tuesday of the week of the A. PH. A. meeting and the Idaho and Montana Pharmaceutical Associations are being invited to hold their meetings at the same time. The meetings of the Oregon and Washington Pharmaceutical Associations will be held on Monday and Tuesday so that their members will be free to attend the A. PH. A. sessions Wednesday, Thursday and Friday.

President Perry of the Oregon Pharmaceutical Association has written that the annual Buyers' Week conducted by the two Portland drug wholesalers has been set for the week of

August 5th and urges that this week be chosen for the A. PH. A. meeting since hundreds of drug store owners from Oregon, Washington, Idaho and even Alaska visit Portland for this Buyers' Week. Dean Mickelsen and the Portland Chamber of Commerce, have written in support of the earlier date. Dean Mickelsen advises that in case the earlier date is chosen, the Multnomah Hotel will give preference to our convention members as to rooms and meeting rooms so that the A. PH. A. meeting will not be interfered with by the larger attendance.

If the members of the Council have comments or suggestions, please submit them promptly as a vote on the local secretary and on the time and headquarters for the meeting will be called for in about ten days.

E. F. KELLY, *Secretary.*

LETTER NO. 5.

To the Members of the Council:

27. Minutes of the First Meeting of the Council. Motion No. 1, Council Letter No. 2, page 846, has received eleven affirmative votes and is carried. President Fischelis is recorded as not voting.

28. Committee on Maintenance. Motion No. 3, Council Letter No. 3, page 849, has been carried and the appointments are approved.

29. Election of Members. Motion No. 4, Council Letter No. 3, page 849, has been carried and applicants numbered 1 to 41, inclusive, are declared elected.

30. Joint Meeting Executive Committee, N. A. R. D. and Council, A. Ph. A. Secretary Dargavel has advised that the annual joint meeting will be held in the Hotel Roosevelt, New Orleans, La., on Monday, September 24th, at 10:30 A.M. All members of the Council are invited to be present and those who expect to attend are requested to notify the secretary as promptly as possible.

The secretary was requested by Mr. Dargavel to suggest the subjects which should be considered at this meeting, and after consulting with the president and chairman of the Council, wrote Mr. Dargavel on August 31st, as per copy attached. Mr. Dargavel has approved this list and advised that, for the present, he has no additions to suggest.

The secretary will appreciate an expression by letter of the views with respect to these subjects of those members of the Council who cannot attend the joint meeting.

E. F. KELLY, *Secretary.*

THE EDUCATION DEPARTMENT OF JAPAN ENCOURAGES SCIENTIFIC RESEARCH.

The department of Education of Japan has decided to grant an official subsidy of 47,000 yen to encourage scientific research for the current year. Among the persons who will receive subsidies for their research work are the following:

Associate Professor Shigehiko Sugazawa (Dr. of Pharmacy) of the Tokyo Imperial University for his study of papaverin compounds.

Professor Takee Tsukamoto of the department of pharmacy in the Imperial College of Medicine at Kanazawa and his associate for his research into the decomposition of anæsthesin.

Professor Etsuo Miyamichi of the Toyoma School of Pharmacy for his study of the disruption of unsaturated fatty acids.

Professor Ryoji Sakai of the Kummamoto School of Pharmacy for his study of food substitutes.

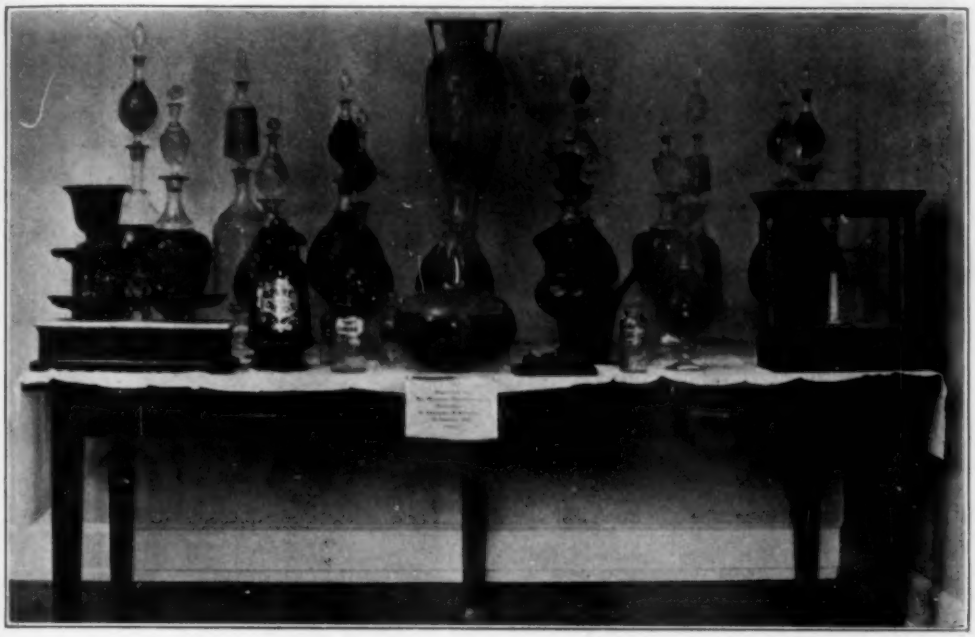
Professor Masanobu Teranishi of the Tokushima Technical Higher School for his study of the alkaloid contained by the root of *Orixa japonica.*

The following persons are to receive subsidies for their studies of chemical problems:

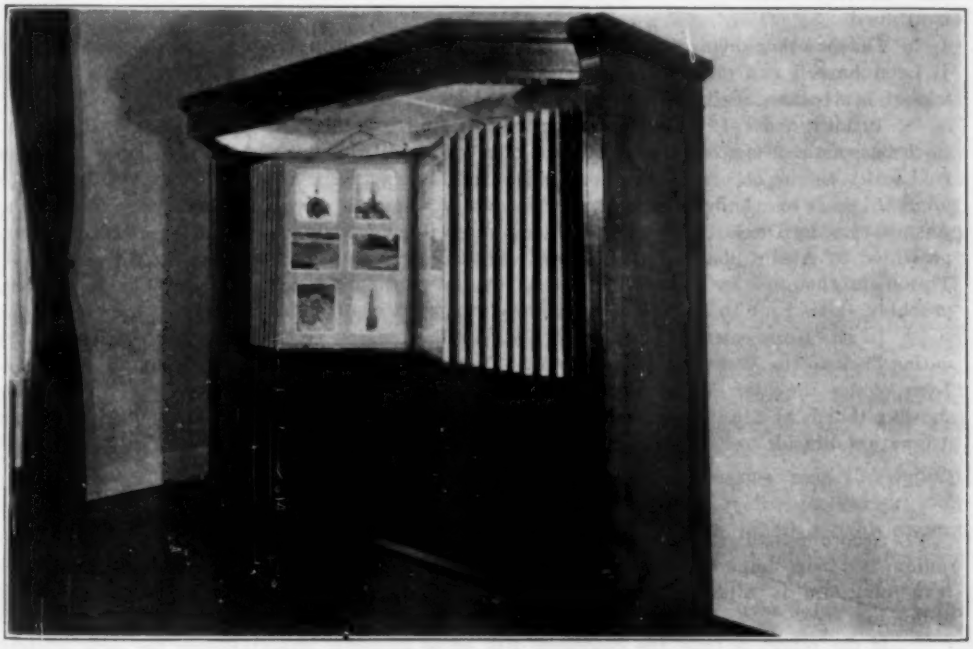
Professor Shoichiro Nagai of the Tokyo Imperial University for his investigation into the relations between the dissolvability of glass and chemical ingredients.

Professor Seigo Minami of the Kyushu Imperial University for his study of the efficacy of vitamin D in skin diseases.

Professor Heihachi Yoshiamara of the Meiji College of Pharmacy for his study of *Ranunculaceæ* and related plants.



Show globes, bottles, jars and balances presented by pharmacist Lawrence Williams of Baltimore. Mr. Williams has one of the largest collections of show globes in this country.



The multiplex display fixture above, and the photographs, were presented by the University of Minnesota, College of Pharmacy, Frederick J. Wulling, Dean. The illustrations are excellent and are displayed under twenty divisions, including the drying ovens, milling and cleaning apparatus, also green houses, drug milling laboratory, medicinal plant laboratory, pharmacognosy laboratory, pharmaceutical laboratory.

A view in the Museum of the American Institute of Pharmacy, AMERICAN PHARMACEUTICAL ASSOCIATION. On top of the case, against the wall, is an early certificate of membership in the AMERICAN PHARMACEUTICAL ASSOCIATION, of the late John F. Hancock. This design was discontinued.

On the other side is displayed a frame of foreign prescriptions filled in the pharmacy of J. Leon Lascoff and presented by him to the ASSOCIATION. In the center, between the two frames, is a balance used in the pharmacy of the late John F. Hancock, of Baltimore.

Inside the case are twenty-two large drug jars, presented by James E. Hancock, of Baltimore. Each one of these jars has a coat of arms of a state, and the name of the drug is on the jar in gold leaf. In the other part of the case is a mortar that came to Maryland more than three hundred years ago and belonged to the family of Governor Stone. It was presented to the ASSOCIATION by Dr. F. B. Tipton. On the same shelf is a framed painting of Texas Bluebonnets, presented by Austin pharmacists. One of the lignum vitæ mortars was presented by Dr. F. B. Tipton and the other by James E. Hancock. On the same shelf is a bottle with a chemical which, probably, dates back to alchemical days, presented by Mrs. H. M. Whelpley.

In the front case is a display of National Formularies, and photostatic copies of letters dating back to the Pharmacopœia of 1820. There is also a book of formulas compiled by Rev. John Wesley, founder of the Methodist Church. The book in the case is of the 26th edition showing that it had been quite widely distributed. There are other items in the exhibit, which it is rather difficult to designate, except by viewing the display.

SYNTHETIC RADIUM.

According to Paris reports and *New York Times* press dispatch, the discovery of synthetic radium has been made by the son-in-law and daughter of the late Mme. Curie, M. and Mme. Jean Joliot, and is to be announced at an international gathering of scientists early next month in London.

If the report is true, the discovery will be of immense importance in the fight against cancer, since it is stated that the artificial product is equally effective as natural radium and can be produced in large quantities comparatively cheaply. The rarity and expensiveness of radium have greatly circumscribed its use in cancer work.

M. and Mme. Joliot for years followed the work of Mme. Curie and are now conducting the laboratory she founded in Paris.

EDITORIAL NOTES

ELEMENT 91—PROTOACTINIUM.

Element 91—named Protoactinium, was isolated by Dr. Aristid V. Grosse at the Kaiser Wilhelm Institute, Berlin in 1927. The element was described in a paper, read by the discoverer, at the recent convention of the American Chemical Society in Cleveland. Dr. Grosse is now of the University of Chicago.

CLAIM TO DISCOVERY OF ELEMENT 93 WITHDRAWN.

There has been considerable interest in the announcement that Odolen Koblic, director of the National Uranium and Radium Plant in Joachimsthal, Czechoslovakia, had discovered a new element, No. 93, to which he proposed to give the name "bohemium." The steps by which the new element can be isolated as a silver salt appeared entirely logical and the working hypotheses sound. Koblic presented his results in a clear, straightforward manner, with unusually complete data, even to an approximate atomic weight of 240.

However, spectroscopic analyses made by experts both at Prague and Berlin show that the scientist was in error in identifying the heavy, difficultly soluble, brilliant yellow product which he isolated as element 93. Following the spectrum and X-ray examination of the salt, it seems certain that it is silver tungstate and, agreeing with the interpretation of the analysis, Koblic has withdrawn his claim of discovery.

In view of the straightforward manner in which this whole incident has come before us, one cannot avoid hoping that Koblic will continue in his research, and if there is an element No. 93 to head the actinium series, that he may be the one definitely to discover it.—*News Edition, Industrial and Engineering Chemistry* (September 10, 1934, page 318).

PHARMACEUTICAL EXHIBIT AT THE CONVENTION OF THE AMERICAN DENTAL ASSOCIATION.

Sponsored jointly by the Revision Committees of the United States Pharmacopœia and National Formulary, an exhibit of official medicines of interest to the dentist was shown at the American Dental Association annual meeting held in St. Paul, Minnesota, August 6 to 10, 1934. More than 4000 dentists were registered. They carried home the idea of Professional Pharmacy and its desire to coöperate in the practice of Dentistry. The display consisted of a central section devoted to chemicals and galenicals official in the U. S. P. and N. F. The display was prepared and exhibited by **Prof. R. E. Terry** of the College of Pharmacy of the University of Illinois.

RECASTING THE NRA.

The NRA is undergoing a change and that is in the direction of having General Johnson coöperate with others and do away with one-man rule. It has been stated that the NRA will be patterned after the American government—executive, legislative and judicial divisions, with the limits and boundaries of each clearly defined; the coöperation of industry and labor, it is stated, will be given positive and consistent direction.

The NRA automatically expires June 16th, the President has announced that the basic ideas will be perpetuated, the problem is under consideration by him, but few details of the proposed revision have been given out.

Announcement has been made of the appointment of a General Code Authority to administer the basic code which covers the 252 industries that have no specific codes; the chairman of this body is Dr. Willard Hotchkiss, president of the Armour Institute of Technology.

THE LONDON PHARMACOPŒIA.

The first London Pharmacopœia was published in 1618. An apothecary was not allowed to dispense or sell drugs unless these had been exposed to public gaze for a number of specified days and any physican had the right to prevent the apothecary from selling drugs or medicines which were in his opinion corrupt or decayed. During the reign of James I a separate charter was granted and only practitioners in pharmacy were admitted to the apothecaries' guild.

Between the years 1618–1851 thirteen editions of the London Pharmacopœia were published, each edition improved on the preceding. There are several copies in the American Institute of Pharmacy, the earliest that of 1653

PERSONAL AND NEWS ITEMS.

The Modern Hospital for August has an article "An Affiliation Plan of Hospitals and the School of Pharmacy" by **Dean Edward Spease,** of the School of Pharmacy, Western Reserve University. Aside from giving the plan there are a number of excellent half-tones showing how the work of the hospital pharmacy is carried on.

Matthias Noll, a verteran among Kansas pharmacists, several years ago, began collecting historical material relating to Kansas pharmacy. This material has been collated and prepared in typewritten form with the purpose of preparing a printed volume dealing with historical pharmacy in Kansas.

N. G. Hubbard, Birmingham, and **John A. Edwards,** Anniston, have been appointed members of the Alabama Board of Pharmacy; the former succeeds **Hal E. Duncan,** resigned, and the latter succeeds the late **W. E. Bingham.** Both of the appointees are active in Association work.

Henry S. Godshall, Lansdowne, Pa., succeeds the late Raymond Hendrickson with Smith, Kline & French Co. Mr. Godshall has been with the firm since his graduation in Pharmacy and is a member of the A. PH. A.

Dr. A. R. Bliss has been named director of the Birmingham Research Laboratories and elected professor of Pharmacology and dean of The School of Pharmacy of Howard College, Birmingham, Ala.

Sir Ronald Storrs, former military governor of Jerusalem, following the World War, was one of the visitors to register at the Pharmacy Exhibit in the Hall of Science at the Century of Progress Exposition. General interest in the exhibit continues unabated with last Sunday one of the best days in the season from the point of registrations by physicians and pharmacists.

Herbert Mayes, former editor-in-chief of the *American Druggist,* has recently been promoted to the editorship of *Pictorial Review.* He is succeeded on the *American Druggist* by Howard Stephenson, former managing editor, with Samuel C. Henry, former secretary of the N. A. R. D., as associate editor.

The new research laboratories of Messrs. Eli Lilly & Co., Indianapolis, will be formally opened with appropriate ceremonies on October 11th. Sir Henry Dale will deliver the main address at the afternoon session. Sir Frederick Banting and Dr. Irving Langmuir will also speak. At the dinner in the evening, addresses will be made by Sir Henry Dale, Dr. Elliott P. Joslin, Dr. George R. Minot, Dr. Frank R. Lillie, Dr. Charles R. Stockard, Dr. George H. Whipple, Dr. Carl Voegtlin and Dr. G. H. A. Clowes, director of the Research Laboratories.

S. L. Hilton has recently donated to the ASSOCIATION a number of volumes from his library and pharmaceutical, chemical and medical publications.

Among recent visitors at the American Institute were A. G. DuMez, W. F. Rudd, A. L. I. Winne, Ernest Little, Clyde W. Graham, Spokane; Paul E. Eliason, Reno; Paul W. Hildebrand, Detroit; Robert William Rodman, New York; W. A. Prout, Charleston; Ernest Bergeron Keen, N. H.; Clyde S. Wills, Richmond. Frequent visits are made by Washington pharmacists and quite a number of architects have inspected the building.

F. J. Steele, of Bloomfield, Pittsburgh, Pa., has donated the following volumes, for which the Association extends thanks: "A Manual of Microscopy," L. K. Darbaker. "Notes on Equation Writing and Chemical and Pharmaceutical Arithmetic," by J. H. Beal. "The Pharmacist and Chemical Record," by N. Gray Bartlett and Albert E. Ebert. "Squibb's Materia Medica," 1906 Edition. "North American Botany," by Amos Eaton and John Wright.

Joseph Calloway, Jr., who has been chief of the New York F. D. A. station since April 1929, has been transferred to Baltimore, and Daniel W. Walsh, chief of the Baltimore station since September 1920, will succeed Mr. Calloway in New York.

Mr. Calloway's transfer to the chiefship of the Baltimore station has been at his own request, according to W. R. M. Wharton, chief of the Eastern district of the Food and Drug Administration. The Eastern district embraces the stations in Atlanta, Baltimore, Boston, Buffalo, New York and Philadelphia. It is one of three districts of the administration and has its headquarters in New York.

Victor E. Levine, professor of biological chemistry and nutrition at Creighton University School of Medicine, and **Charles W. Bauer,** professor of chemistry at the School of Pharmacy, are spending four months in the Arctic in research among the Eskimo children. They are making physical measurements and studies in nutrition. An investigation will be made of the susceptibility of the Eskimo child to tuberculosis, diptheria and scarlet fever.

OBITUARY.

RAYMOND HENDRICKSON.

Raymond Hendrickson, Chester, Pa., member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1917, died suddenly while on his vacation in Ocean City, N. J., on August 7th.

Mr. Hendrickson was born in California on November 12, 1878, but came east at an early age and entered the retail drug business. He was graduated from the Philadelphia College of Pharmacy and Science in 1902. He successfully owned retail drug stores in Carlisle and Chester, which he sold at the time he entered the employ of Smith, Kline & French Co., of Philadelphia.

He was a charter member and one of the founders of the Phi Theta Sigma Fraternity and was an honorary member of the Holland Club of New York. He was also a member of the Philadelphia Kiwanis Club, Delaware County Druggists' Association, Philadelphia Association of Retail Druggists, Pennsylvania Pharmaceutical Association, Drug Club of Veterans, Traveling Men's Association of the Pennsylvania Pharmaceutical Association and National Travel Club.

Mr. Hendrickson made his home at Twenty-first Street and Providence Avenue, Chester, Pa. He is survived by his widow, and daughter, Dorothy Jane Hendrickson.

VAN AMBURG SANDLES.

Van Amburg Sandles, of McKees Rocks, Pa., member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1909, died Tuesday, August 14th. He had been in ill health for about three years but was seriously ill only during the last two weeks.

Mr. Sandles was born at Wexford, March 20, 1876, son of the late Mr. and Mrs. William H. Sandles. He was educated in the public schools of Beaver Falls, afterward attended the Pittsburgh College of Pharmacy, where he was graduated in 1896.

Mr. Sandles came to McKees Rocks in 1900. He was prominently identified with the business, religious and social life of the borough and community. He operated a drug store at 1000 Chartiers Avenue since 1907 and was deeply interested in his profession. He was a member of Allegheny County Retail Druggists' Association and the Pennsylvania Pharmaceutical Association, and a regular attendant at the annual conventions of the latter.

He was a member of the Masonic bodies and of the Presbyterian Church of McKees Rocks. Mr. Sandles is survived by his widow, Mrs. V. A. Sandles, and one son, William W. Sandles.

We are advised of the death of the mother of our fellow-member, **Dr. S. E. Massengill,** Bristol, Tenn. Mrs. Massengill died September 6, 1934, aged 86 years.

DEATH OF THE TREASURER OF THE BRITISH PHARMACEUTICAL SOCIETY.

A. H. Jenkin, treasurer of the British Pharmaceutical Society since 1931, died suddenly on August 24th, of angina pectoris, aged sixty-three years.

During the war Mr. Jenkin was one of the promoters of the Pharmacists' Volunteer Corps in which he was platoon commander. He was active in pharmaceutical organizations and is known in connection with the case of Jenkin *vs.* The British Pharmaceutical Society (1920).

The Jenkin Test Case.

The suit was brought to test in court whether the British Pharmaceutical Society could engage in certain activities which seemed desirable to some. The judgment declared that it was not within the objects, powers or purposes of the Society to undertake or perform any of the following:

"(1) To regulate the hours of business of members of the Society; (2) To regulate the wages and conditions of employment as between masters and their employees who are members of the Society; (3) To regulate the prices at which members shall sell their goods; and (4) To insure and to effect insurances of members of the Society against errors, neglect, and misconduct of employees and against fire, burglary, damage to plate glass, and generally against insurable risks or to spend any part of its funds upon the promotion, establishment and work of the Industrial Council Committee for the drug trade or industry."

One result of the *Test Case* was the formation of the Retail Pharmacists' Union.—*Journal and Pharmacist* (September 1, 1934).

For a number of years Mr. Jenkin owned a pharmacy, but for a longer period was engaged in hospital service; he served as chief pharmacist at the City of London and East London Dispensary until his death.

SOCIETIES AND COLLEGES.

DISTRICT OF COLUMBIA PHARMACEUTICAL ASSOCIATION.

The election of officers of the District of Columbia Pharmaceutical Association will be held at its next session, in October. The *President* of the Association is Bert A. Smyser and the *Secretary* is Augustus C. Taylor.

DELAWARE STATE PHARMACEUTICAL SOCIETY.

The forty-eighth annual meeting of Delaware Pharmaceutical Society was held at Rehoboth Beach, June 27th–28th. Among the speakers were Dr. George L. Secord and Andrew F. Ludwig, President of the Maryland Pharmaceutical Association.

The following officers were elected: *President*, Harry Jones, Smyrna; *First Vice-President*, George W. Brittingham, Wilmington; *Second Vice-President*, William B. Jester, Delaware City; *Third Vice-President*, Edward J. Elliott, Bridgeville; *Secretary*, Albert Dougherty, Wilmington; *Treasurer*, Albert Bunin, Wilmington.

NEBRASKA PHARMACEUTICAL ASSOCIATION.

Nebraska Pharmaceutical Association will hold its 1935 convention in Lincoln during the month of February while the State Legislature is in session. Work on the program for the meeting is well under way.

NEW JERSEY PHARMACEUTICAL ASSOCIATION.

One of the most interesting conventions of the New Jersey Pharmaceutical Association, was held at Asbury Park, June 12th to 15th. Among the speakers were: President R. P. Fischelis of the AMERICAN PHARMACEUTICAL ASSOCIATION and Dr. Ernest Little, of the Pharmacy Department Rutgers University.

The report of the Committee on Pharmaceutical Education and Standards was presented by Chairman Fischelis.

An interesting feature of the meeting was the presentation of the Pharmacy Week trophy donated by the Hudson County Retail Druggists Association and won by John H. Hoagland of New Brunswick; of the features, one was the display of native medicinal drugs.

The following officers were elected to serve for the ensuing year: *President*, David I. Cohen, Jersey City; *First Vice-President*, Harry B. Reibel, Elizabeth; *Second Vice-President*, Benjamin Schamach, Paterson; *Secretary*, Prescott R. Loveland, 214 Chelsea National Bank Building, Atlantic City; *Treasurer*, Charles J. McCloskey, Branchville.

TENNESSEE PHARMACEUTICAL ASSOCIATION.

Tennessee Pharmaceutical Association held an interesting meeting at Knoxville, July 17th to 19th. The NRA was endorsed and a plan for constructive legislation was adopted. The following officers were elected: *President*, Robert R. Ferrell, Memphis; *First Vice-President*, L. S. Elgin, Knoxville; *Second Vice-President*, Phil P. Vance, Chattanooga; *Third Vice-President*, Wm. P. Winter, Nashville; *Treasurer*, Homer J. Berryhill, Jackson.

At a meeting of the State Executive Board, held in Nashville, August 20th, **Tom C. Sharp** of Nashville was elected *Secretary*.

TEXAS PHARMACEUTICAL ASSOCIATION.

The Texas Druggist, official organ of the Association, for September, reports its 55th annual meeting. The veterans elected Frank B. Dwyer, with a business record of 56 years, president.

A committee will be appointed by President Seeley for the purpose of studying the Pharmacy Law of Texas with a view of making such changes as will enhance public health and benefit all connected with pharmacy.

Dr. W. J. Danforth, Fort Worth, has been appointed field secretary, whose duty is to contact with Texas pharmacists.

Lee Stinson now wears a past-president's badge of Texas Pharmaceutical Association. The members of the Executive Committee are: *President*, A. H. Seeley; *Vice-Chairman*, Shine Philips; John B. Ray, Henry F. Hein, H. P. Gaddis, E. B. Oliver, J. C. Frazier, Walter F. Adams, *Secretary*.

NATIONAL WHOLESALE DRUGGISTS' ASSOCIATION.

Among the speakers invited to address the convention of the National Wholesale Druggists' Association to be held October 1st–6th, at White Sulphur Springs, W. Va., are representatives of the Food and Drug Administration, the Federal Trade Commission and the Na-

tional Recovery Administration. It is hoped that General Hugh S. Johnson, National Recovery Administrator, will be present as a speaker.

At the present convention, an innovation will be introduced. In the past it has been the custom for chairmen of the various committees of the association to read detailed reports of their activities during the year preceding the convention. At the present meeting, these reports will not be read, they will be printed and, as each visitor at the convention registers, he will be given a complete set of the reports.

Reports which are controversial in any respect will be read in abstract at some of the sessions of the convention, to afford an opportunity for discussion and questioning from members listening in.

Pharmacy Exhibit at Century of Progress.

The photograph shown herewith was taken on September 17th (Constitution Day). While the number of visitors on this occasion was larger than usual, the average attendance at the Pharmacy Exhibit compared favorably with that of other exhibits and shows that the public is interested in the service of pharmacy.

BARBITURIC ACID POISONING.*

It is pointed out by Purves-Stewart and Wilcox (London) that while there is no objection to the administration of barbiturates under medical supervision, their repeated daily administration over long periods in hypnotic doses is not always free from danger, and may induce toxic symptoms in the central nervous system. Persons addicted to the daily use of these drugs not uncommonly take a dangerous overdose, accidentally or otherwise. The barbiturates should be obtainable, they say, only on medical prescription, which should not be repeated without authority. Several cases are cited showing that acute barbitone coma is materially improved by cisternal drainage, a method which should be borne in mind as supplementary to other measures.—*The Prescriber* (September 1934), 288.

* J. Purves-Stewart and W. Wilcox, "Cisternal Drainage in Coma from Barbitone Poisoning," *Lancet* (March 10, 1934), 500–503.

LEGAL AND LEGISLATIVE.

THE CODE OF FAIR COMPETITION AMENDED.

A public hearing was held on June 7, 1934, on the Amendment (Loss Limitation Provision) as signed April 8, 1934—see April JOURNAL, A. PH. A., page 382. The National Retail Drug Code Authority requested a continuation of the Amendment with the elimination of the proviso referring to discounts, free deals and allowance. This proviso has been omitted in the Amendment signed on September 21, 1934, which follows. In its stead the Administrator is given certain powers to be exercised in any particular case where unfair advantage is being taken of the Amendment.

AMENDMENT TO THE CODE OF FAIR COMPETITION FOR THE RETAIL TRADE—APPROVED SEPTEMBER 21, 1934, EFFECTIVE IMMEDIATELY.

Section 6 of Schedule "A" of the Code of Fair Competition for the Retail Trade, as amended, is hereby amended as follows:

Section 6. It is hereby declared an unfair trade practice for any drug retailer to sell any drugs, medicines, cosmetics, toilet preparations or drug sundries at a price below the manufacturers' wholesale list price per dozen; provided, however, that in the case of biologicals or other of the above-mentioned products, which are not customarily sold in dozen or greater lots, the Code Authority may fix a comparable unit quantity.

The Administrator, at the recommendation of the National Retail Drug Code Authority or otherwise, after such notice and hearing as he may deem necessary, may suspend or modify the operation of this clause at any time when it appears that such operation does not tend to effectuate the purposes of Title I of the Act. The Administrator shall suspend or modify the operation of this clause in any particular case where a manufacturer is found to be manipulating his prices because of this provision in such a manner as to maintain an unwarrantedly higher price to the ultimate consumer or to oppress small enterprises, or otherwise to defeat the purposes of the Act.

RELIEVES SMALL BUSINESS FROM PAYING MULTIPLE ASSESSMENTS.

The National Recovery Administration has taken a further step toward relieving wholesalers and particularly, small retailers, from paying multiple assessments. An Administrative Order issued by the National Recovery Administrator puts a stop, until an improved formula can be worked out, to collections by Code Authorities governing one of wholesale or retail distribution from wholesalers or retailers who deal principally in some other line.

The variety of merchandise handled by the small local store, or the general store which sells "anything the farmer needs"—types which are important factors in the total retail business—bring their operations under a number of Codes. The local store owner has been harassed by demands to pay assessments to all of those Code Authorities. Department stores and wholesale distributors also are importantly affected. Under the order issued to-day, they will pay assessments only to the Code Authority for the Code governing their principal line of business, with few exceptions.

PLAN TO MAKE ORDER PERMANENT.

While the present order is temporary, the National Recovery Administration now is working out a plan to make permanent both its general principle and its main features. The permanent plan will provide, at the same time, for the adequate support of Code Authorities governing the distribution of merchandise sold through stores handling other products as their principal line.

It was pointed out that where a wholesaler or retailer is also engaged in some other line of business, such as manufacturing, this order will not prevent collection of assessment on the other business by the Code Authority for that business.—From *Blue Eagle*.

NEW JERSEY CODE.

Article 9 of the New Jersey act would create an Industrial Advisory Council composed of five members to be appointed by the governor to represent labor, industry and the public. One of the three representatives of the consuming public would be chairman of the group. The council would act as a price-fixing commission. Upon petition from the administrator, it would investigate complaints of unfair competition. This council would have the power to establish price fixing in industries in which investigation showed this method was necessary in order to protect the business of the industries' members.

Another section of the act would authorize the administrator to appoint a planning and research division to analyze wage and labor conditions, investigate and analyze costs of operation of trades and industries where minimum prices are requested: coöperate with the Industrial Recovery Council and furnish statistical and other data to the Administrator.

LIABILITY OF A DRUGGIST IN COMPOUNDING PRESCRIPTIONS.

A physician prescribed for the plaintiff a 1 per cent solution of gentian violet, the written prescription directing the use of the solution as a mouth wash. The physician, however, orally directed the plaintiff to use the solution in her eyes also. The drug company to which the plaintiff took the prescription gave her, not a 1 per cent solution of gentian violet, but a 3 per cent solution, and this, when used as an eyewash, caused the plaintiff to lose her eyesight. She sued the drug company. The trial court sustained the demurrer interposed by the drug company. The plaintiff then appealed to the Court of Appeals, and the judgment of the trial court was reversed.

JAPAN PHARMACISTS UNION WANTS BETTER CONTROL OF NARCOTIC SALES.

As a result of the action of the Japan Pharmacists Union, a recommendation was addressed to Baron Tatsuo Yamamoto signed by President Kametaro Kawai of the Union. There seems to be an increasing tendency to the use of narcotics and while there have been more violations by pharmacists it has been largely due to the fact that those who seek to secure narcotics intimidate the pharmacists and not because the pharmacists desire to sell narcotics.

In the petition sent to the government it is suggested that sanatoriums be established, that drug addicts be registered; that local limitations be placed on the use and quantities of prescribed narcotics and that uniform narcotic prescriptions be established, also that there be better control of handling narcotics by unqualified persons.

PROPOSED REVISION OF THE REGULATION OF DANGEROUS DRUGS IN JAPAN.

The basic aim of the proposed revision of the narcotic regulations is to prevent the abusive use of narcotics and the following measures have been advanced:

1. To expand the definition of narcotics.
2. To replace the existing system of registration by a permit system.
3. To require physicians to report narcotic addicts they have treated and to place stricter control on their issuance of prescriptions and to inflict severer punishment on violators of regulations.

The following are the principal items of the proposed revision:

Article 1. Narcotics in these regulations include the following:

1. Morphine, diacetylmorphine and other morphine esters and salts.
2. Crude morphine, coca leaves and crude cocaine.
3. Ecugonine, cocaine and other ecugonine esters and salts.
4. Dihydro-oxycodeinon, dihydro-codeine, in dihydro-morphinon, acetyl-dihydro-codeine, dihydromorphine and other esters and salts.
5. Codeine, ethyl morphine, benzyl-morphine and other morphine esters and salts.
6. 5-nitro-morphine and its derivatives.
7. Dihydro-codeine and tebine and their salts.
8. Diacetyl-morphine and those containing 20 per cent or more of morphine and ester (excepting diacetyl-morphine, codeine, ethyl-morphine).
9. Those containing 0.2 or more per cent of the following: dihydro-oxycodeinon, dihydro-codeinon, dihydromorphinon, acetyldihydro-codeinon, dihydro-morphine or their esters, 5-nitro-morphine and derivatives.
10. Those containing ecugonine or cocaine and their ecugonine esters, their amount being 0.1 or more per cent.
11. Indian hemp or those containing its resin.

THE LABORATORY.

O. U. Sisson, Chicago, who was the Pharmacy Week prize-winner last year, has donated the picture of "The Laboratory" which was used as the background of his Window. It is about 5 feet high and 7 feet wide, a Hollywood production by Pathé. The ASSOCIATION thanks Mr. Sisson for his donation which has been placed in the Museum of the American Institute of Pharmacy.

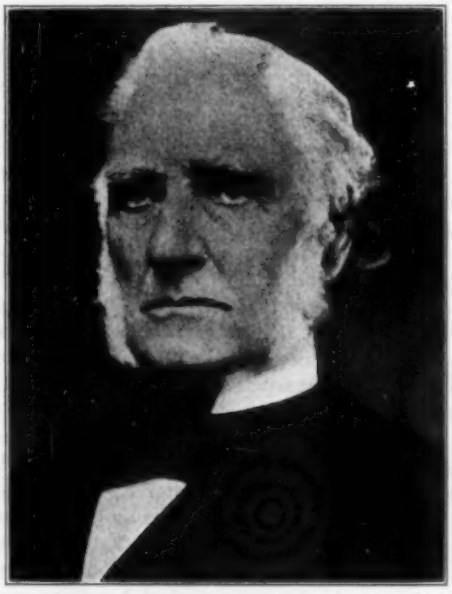
BOOK NOTICES AND REVIEWS.

"Aan P. van der Wielen." D. B. CENTEN'S Uitgeversmaatschappij N. V. Amsterdam. 1934. 205 pages. The students and friends of European teachers have a happy custom of issuing a "festschrift" when a teacher has completed a certain number of years of service. This particular brochure is dedicated to Professor P. van der Wielen upon the completion of his twenty-fifth year as professor of pharmacy at the University of Amsterdam. Twenty of Professor van der Wielen's former students have each contributed a piece of original research in his honor. These monographs are bound together with a tribute to Professor van der Wielen and a summary of his publications numbering eight books, twelve pamphlets and several hundred contributions to journals. The space allowed the reviewer barely warrants more than the mention of the titles of the twenty monographs. They are as follows: (1) The Bacteriological Nature of Bread (W. C. de Graaf); (2) A Review of the Standards for Alcohol (D. van Os); (3) A New Oxidation and Synthesis in the Dog-Kidney (I. Snapper and A. Grunbaum); (the isolated dog-kidney has been found to oxidize phenyl propionic acid to cinnamic acid which separates in combination with glycocol as cinnamoyl-glycocol); (4) Pharmaceutical Investigation of Digitalis Leaves by the Aid of Biological Methods (U. G. Bijlsma); (5) The Forming of Exotoxins by Staphylococcus (E. W. Walch); (6) New Applications of Old Truths in Documentary Research (C. J. van L. Hulsebosch); (7) Contribution to the Investigation of Fruit Lemonade Syrup (C. Bakker); (8) The Merchandise Marks Act and the Price of Medicines (K. Holm); (9) The Investigation of Various Kinds of Balsam Copaiba (J. W. Birza); (10) The Blood-Sucker as a Toxicological Test Animal (J. T. Groll); (11) The Determination of Hexamethylenetetramine in Anhydromethylene Citric Acid Hexamethylene-tetramine (Helmitol-Bayer) (M. J. Schulte); (12) The Quantitative Colorimetric Determination of Meconic Acid in Opium by Means of the Stufen Photometer. (C. G. van Arkel); (13) The International Method for the Determination of Morphine in Opium (E. C. M. J. Hollman); (14) Rhizome and Extract of Aspidium (J. Kok); (15) East-Indian Poisons (C. J. Blok); (16) The Behavior of Various Acids in Relation to Cinchona Tannins (E. W. Ansingh); (17) A Colorimetric Determination for Cysteine (E. Hazeloop); (18) Exterior Influences upon the Crystallization of NaCl (H. D. van Oort); (19) Influence of Glucose upon the Rotation of Blood Serum of Patients in Health; with Hyperglycæmia and Others (G. Sant); (20) Standardized Sieves (P. Spaander).—ELMER H. WIRTH.

We are in receipt of reprints: "Report on Preservatives," *Journal of the Association of Official Agricultural Chemists*, John C. Krantz, Jr. "Utilization of Inulin from Arctium Lappa and Certain Soluble Inulins by the Rat," by C. Jelleff Carr and John C. Krantz, Jr., *Department of Pharmacology, School of Medicine, University of Maryland*.

AMERICAN HOSPITAL ASSOCIATION.

The American Hospital Association Conference will be held in Philadelphia, September, 24th–28th. The Hospitals Libraries' Round Table will be held on Tuesday, September 25th, with Mr. Robert E. Neff, Administrator, University Hospitals, State University of Iowa, Iowa City, Iowa, acting as Chairman.



PHILO CARPENTER.

(See page 922, JOURNAL A. PH. A., 1931.)

In the Pharmacy Exhibit, Century of Progress, is a reproduction of the first Chicago Pharmacy, owned by Philo Carpenter, opened in 1832. A collection of materials and utensils of the period are shown.